Neurofibromatosis type 1 and related disorders

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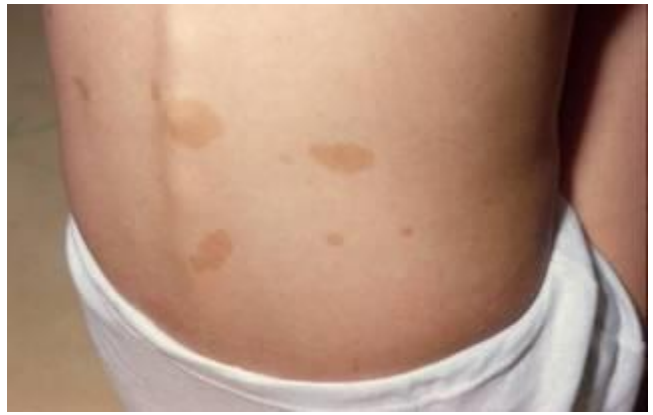
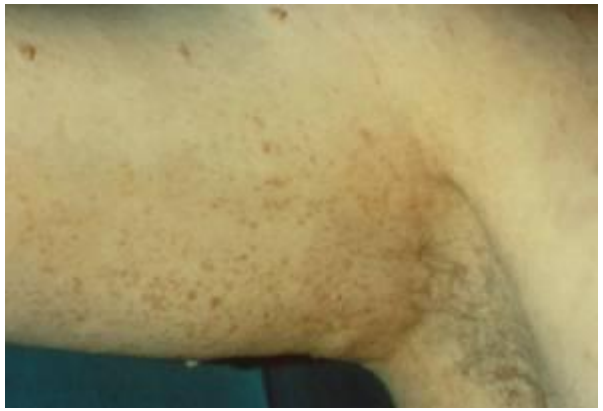
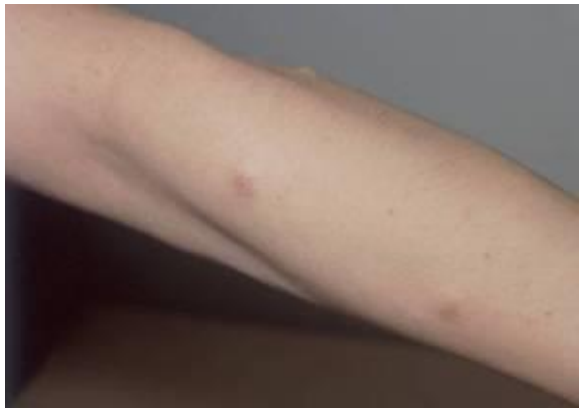
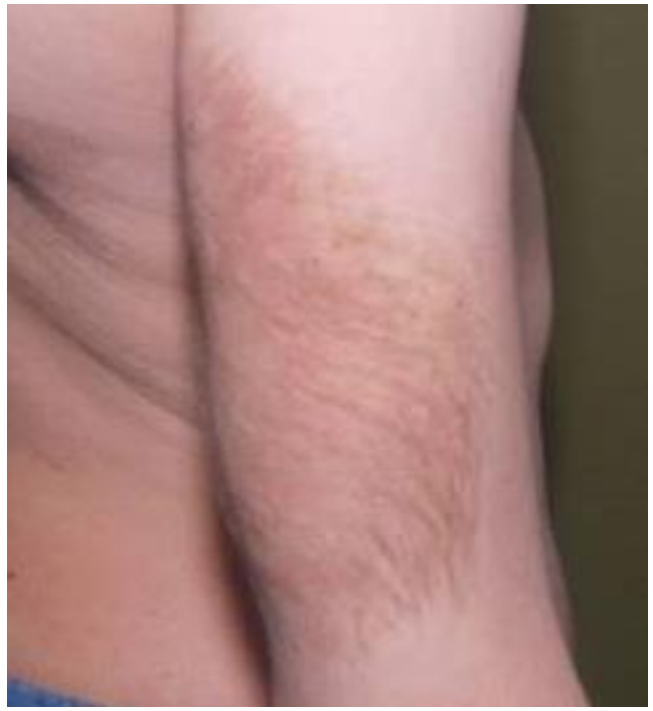
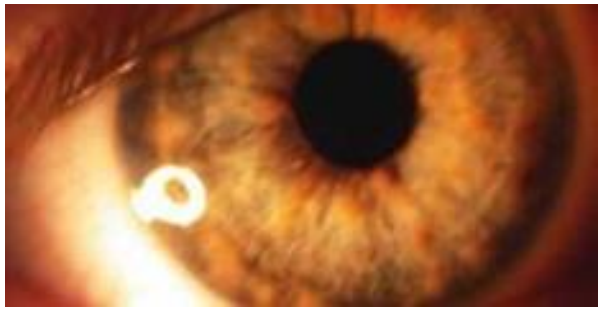
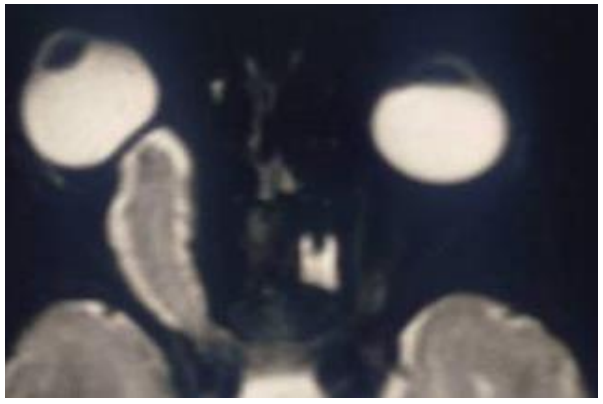
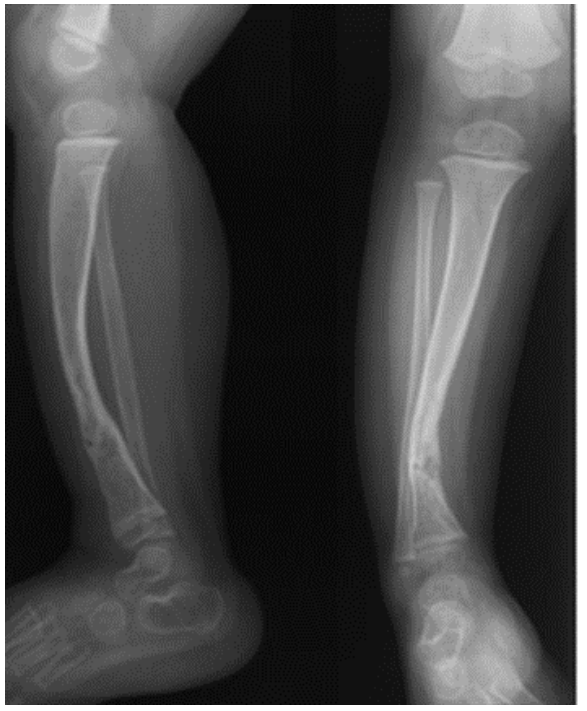
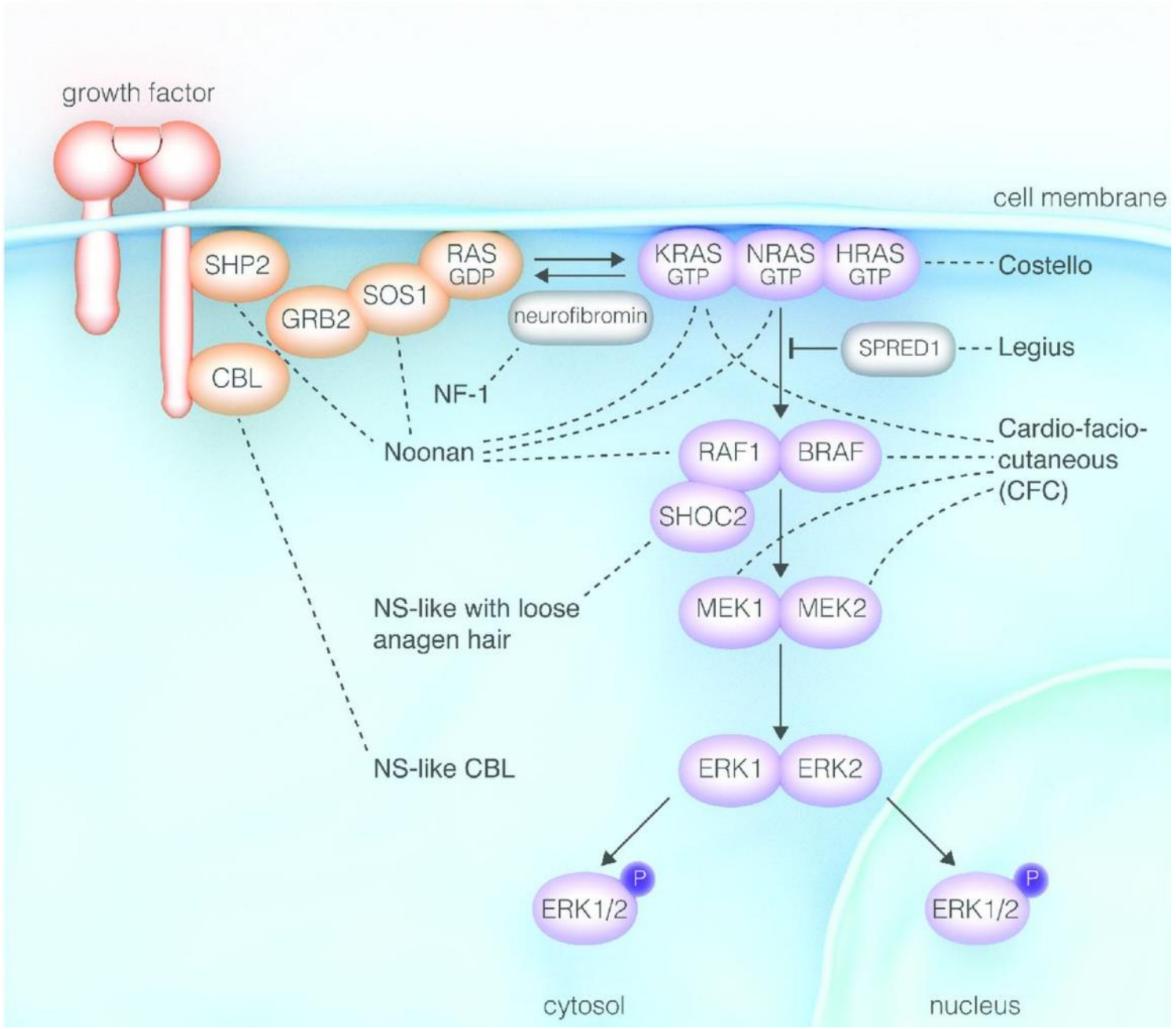
Neurofibromatosis type 1
NIH diagnostic criteria

- Six or more café-au-lait macules (>5 mm diameter in children, >15 mm in adults)
- Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma
- Axillary or inguinal freckling
- Optic-pathway glioma
- Two or more Lisch nodules
- Bone dysplasia
- First-degree relative with neurofibromatosis type 1



Charlotte M. Niemeyer, Haematologica, 2014, 99: 1653-1662.

NF1 is a tumour suppressor gene

Biallelic *NF1* inactivation

- Tumour formation (benign and sometimes malignant)
  - Glial cells (astrocytoma)
  - Schwann cells (neurofibroma)
  - Interstitial cells of Cajal (gastrointestinal stromal tumour)
  - Glomus cells in digits (glomus tumour of finger)
  - Chromaffin cells of adrenal gland (pheochromocytoma)
  - Bone marrow (JMML)
  - Malignant peripheral nerve sheath tumour (MPNST)
- Non-tumoral features
  - Congenital bowing of bones with/without pseudarthrosis
  - Café-au-lait spots

- Increased RAS-MAPK signalling

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study

SHRUTI GARG[1] | ANNUKKA LEHTONEN[2] | SUSAN M HUSON[2] | RICHARD EMSLEY[3] | DOROTHY TRUMP[2] | D GARETH EVANS[2] | JONATHAN GREEN[1,4]

Minimum prevalence of 25% of ASD DSM-IV-TR

NF1 has become a monogenic model to study autism

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Prevalence of Autism Spectrum Disorder Symptoms in Children With Neurofibromatosis Type 1

Ellen Plasschaert,[1,2] Mie-Jef Descheemaeker,[2,3] Lien Van Eylen,[3,4,5] Ilse Noens,[3,4] Jean Steyaert,[2,3,5,6]* Eric Legius[1,2]

JAMA Psychiatry | Original Investigation

Disease Burden and Symptom Structure of Autism in Neurofibromatosis Type 1

A Study of the International NF1-ASD Consortium Team (INFACT)

Stephanie M. Morris, MD; Maria T. Acosta, MD; Shruti Garg, PhD; Jonathan Green, FRCPsych; Susan Huson, MD; Eric Legius, MD; Kathryn N. North, MD; Jonathan M. Payne, PhD; Ellen Plasschaert, PhD; Thomas W. Frazier, PhD; Lauren A. Weiss, PhD; Yi Zhang, MSc; David H. Gutmann, MD, PhD; John N. Constantino, MD

- 531 individuals (2.5 – 84 y) from 6 NF1 clinical centers.
- Autistic symptomatology demonstrated a robust unitary factor structure
- Strong but separable relationship with ADHD symptoms
- Within-family correlation far exceeded that observed in the general population and ASD family samples.

Morris et al., JAMA Psychiatry, 2016

Summary Nf1 mouse learning

Alcino Silva laboratory

- Hippocampal and prefrontal learning deficits
- Increased inhibition by GABAergic interneurons
  - Impaired long term potentiation (decreased synaptic plasticity)
  - Impaired hippocampal dependent learning
- Normal learning in adult mice by acutely reducing Ras signalling
  - Farnesyl transferase inhibitors (farnesyl needed to anchor RAS in cell membrane)
  - Lovastatin (cholesterol lowering drug, also lowering of farnesyl synthesis)

Costa et al., Nature, 2002
Li et al., Curr Biol, 2005
Shilyansky et al., PNAS, 2010

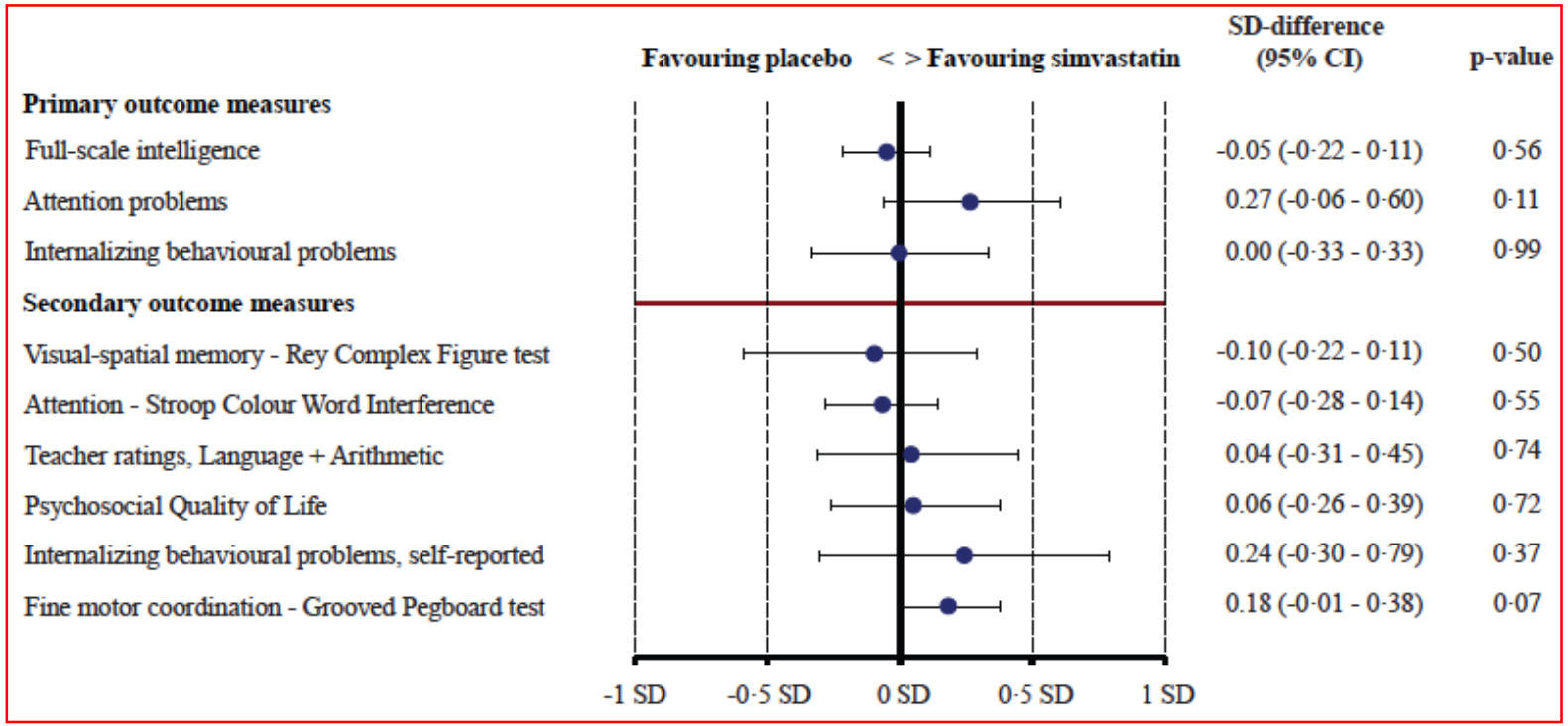
Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial

Thijs van der Vaart, Ellen Plasschaert, André B Rietman, Marleen Renard, Rianne Oostenbrink, Annick Vogels, Marie-Claire Y de Wit, Mie-Jef Descheemaeker, Yvonne Vergouwe, Coriene E Catsman-Berrevoets, Eric Legius, Ype Elgersma, Henriëtte A Moll

Lancet Neurol 2013; 12: 1076–83

Published Online
October 1, 2013
http://dx.doi.org/10.1016/
S1474-4422(13)70227-8

12 months of treatment
8-16y
84 children



Randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1

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Nicole J. Ullrich, MD, PhD
Alan Cantor, PhD
Stephen J.C. Hearps, PGDip
Gary Cutter, PhD
Tena Rosser, MD
Karin S. Walsh, PsyD
Gerard A. Gioia, PhD
Pamela L. Wolters, PhD
James Tonsgard, MD
Elizabeth Schorry, MD
David Viskochil, PhD
Laura Klesse, PhD, MD
Michael Fisher, MD
David H. Gutmann, MD, PhD
Alcino J. Silva, PhD
Scott J. Hunter, PhD
Celiane Rey-Casserly, PhD
Nancy L. Cantor, PhD

ABSTRACT

Objective: To assess the efficacy of lovastatin on visuospatial learning and attention for treating cognitive and behavioral deficits in children with neurofibromatosis type 1 (NF1).

Methods: A multicenter, international, randomized, double-blind, placebo-controlled trial was conducted between July 2009 and May 2014 as part of the NF Clinical Trials Consortium. Children with NF1 aged 8–15 years were screened for visuospatial learning or attention deficits (n = 272); 146 children demonstrated deficits at baseline and were randomly assigned to lovastatin (n = 74; 40 mg/d) or placebo (n = 70). Treatment was administered once daily for 16 weeks. Primary outcomes were total errors on the Cambridge Neuropsychological Test Automated Battery Paired Associate Learning task (visuospatial learning) and the Score subtest from the Test of Everyday Attention for Children (sustained attention). Secondary outcomes measured executive function, attention, visuospatial skills, behavior, and quality of life. Primary analyses were performed on the intention-to-treat population.

Results: Lovastatin had no significant effect on primary outcomes after 16 weeks of treatment: visuospatial learning (Cohen $d = -0.15$, 95% confidence interval −0.47 to 0.18) or sustained attention (Cohen $d = 0.19$, 95% confidence interval −0.14 to 0.53). Lovastatin was well tolerated, with no increase in reported adverse events compared to placebo.

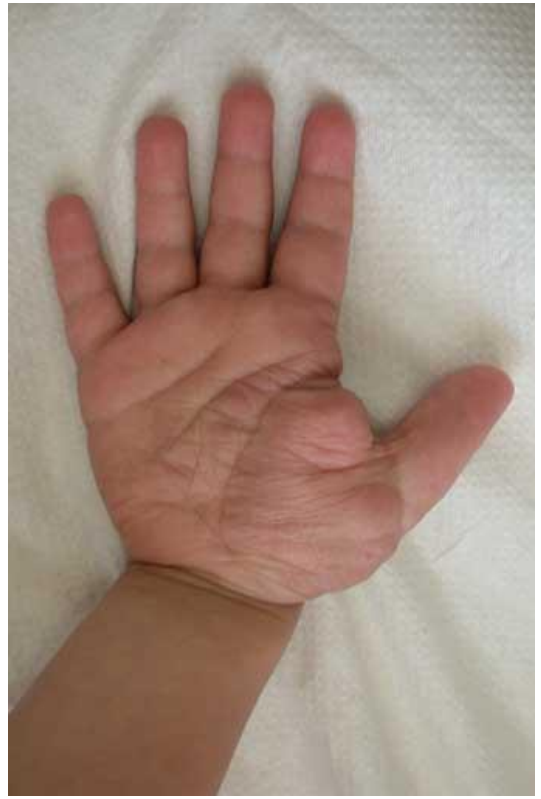
Conclusions: Lovastatin administered once daily for 16 weeks did not improve visuospatial learning or attention in children with NF1 and is not recommended for amelioration of cognitive deficits in this population.

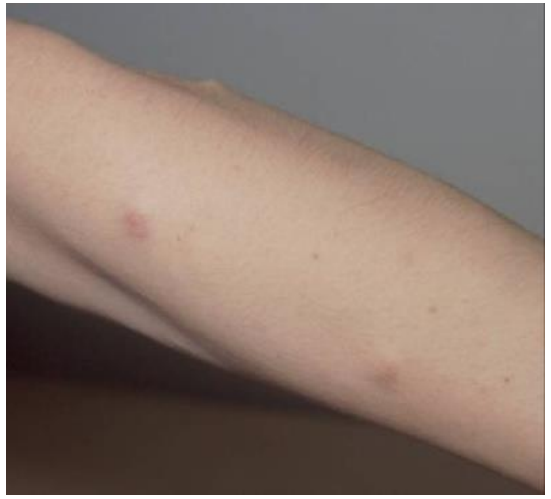
ClinicalTrials.gov identifier: This study was registered at ClinicalTrials.gov (NCT00853580) and Australian New Zealand Clinical Trials Registry (ACTRN12607000560493).

Classification of evidence: This study provides Class I evidence that for children with NF1, lovastatin does not improve visuospatial learning or attention deficits. *Neurology*® 2016;87:2575–2584

Neurofibromas

- Neurofibroma formation
  - Importance of timing
    - Plexiform neurofibroma
      - Second hit in Schwann cell precursors during foetal development
      - Zheng et al, 2008.
    - Dermal neurofibroma
      - Second hit postnatal in “skin derived precursor cells” (SKPs) in mouse model for dermal neurofibromas
      - Le et al, 2009





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

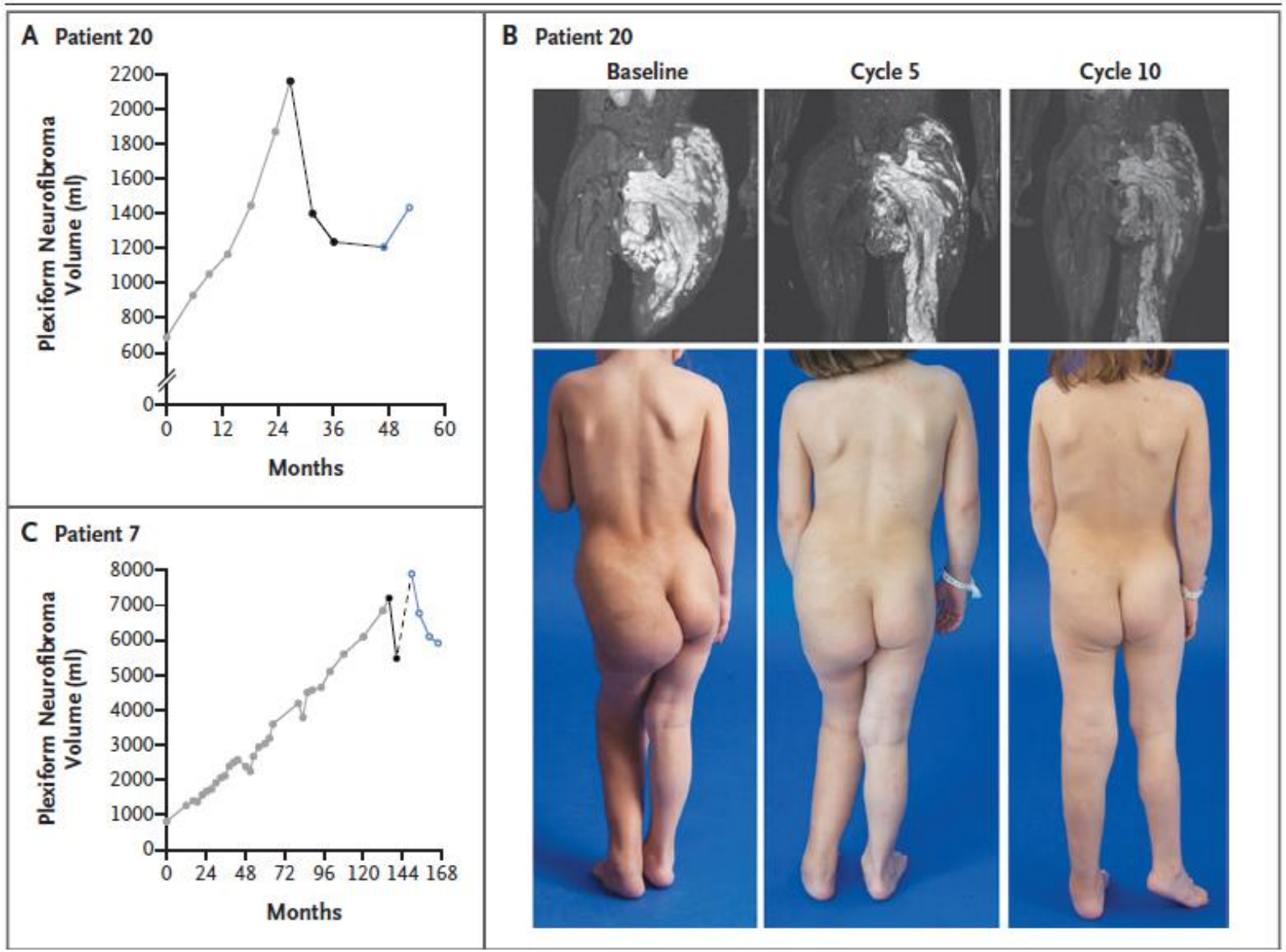
Activity of Selumetinib in Neurofibromatosis Type 1–Related Plexiform Neurofibromas

Eva Dombi, M.D., Andrea Baldwin, C.P.N.P., Leigh J. Marcus, M.D., Michael J. Fisher, M.D., Brian Weiss, M.D., AeRang Kim, M.D., Ph.D., Patricia Whitcomb, R.N., Staci Martin, Ph.D., Lindsey E. Aschbacher-Smith, M.S., Tilat A. Rizvi, Ph.D., Jianqiang Wu, M.D., Rachel Ershler, M.D., Pamela Wolters, Ph.D., Janet Therrien, B.S., John Glod, M.D., Ph.D., Jean B. Belasco, M.D., Elizabeth Schorry, M.D., Alessandra Brofferio, M.D., Amy J. Starosta, Ph.D., Andrea Gillespie, R.N., Austin L. Doyle, M.D., Nancy Ratner, Ph.D., and Brigitte C. Widemann, M.D.

RESULTS

A total of 24 children (median age, 10.9 years; range, 3.0 to 18.5) with a median tumor volume of 1205 ml (range, 29 to 8744) received selumetinib. Patients were able to receive selumetinib on a long-term basis; the median number of cycles was 30 (range, 6 to 56). The maximum tolerated dose was 25 mg per square meter (approximately 60% of the recommended adult dose). The most common toxic effects associated with selumetinib included acneiform rash, gastrointestinal effects, and asymptomatic creatine kinase elevation. The results of pharmacokinetic evaluations of selumetinib among the children in this trial were similar to those published for adults. Treatment with selumetinib resulted in confirmed partial responses (tumor volume decreases from baseline of ≥20%) in 17 of the 24 children (71%) and decreases from baseline in neurofibroma volume in 12 of 18 mice (67%). Disease progression (tumor volume increase from baseline of ≥20%) has not been observed to date. Anecdotal evidence of decreases in tumor-related pain, disfigurement, and functional impairment was observed.

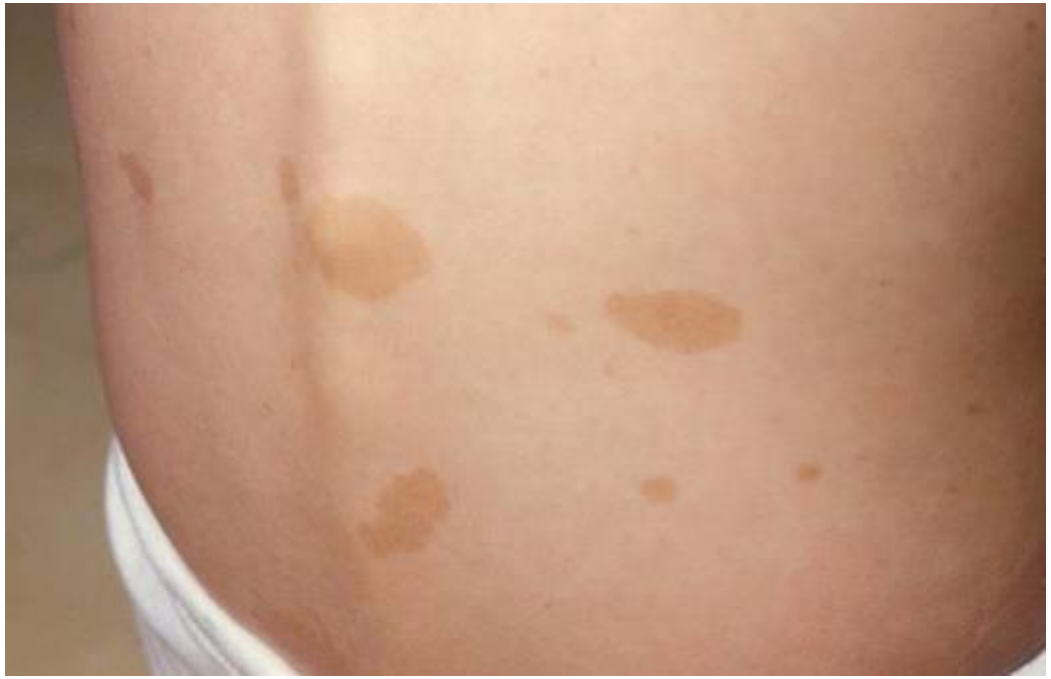
NEJM December 29, 2016



NEJM December 29, 2016

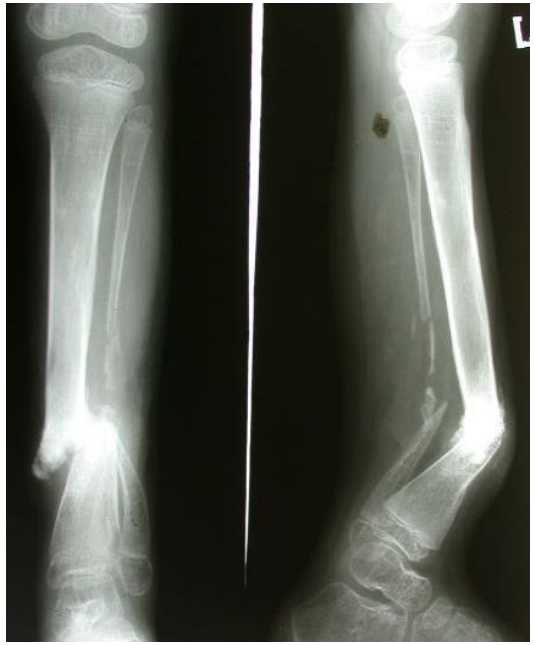
Café-au-lait spots

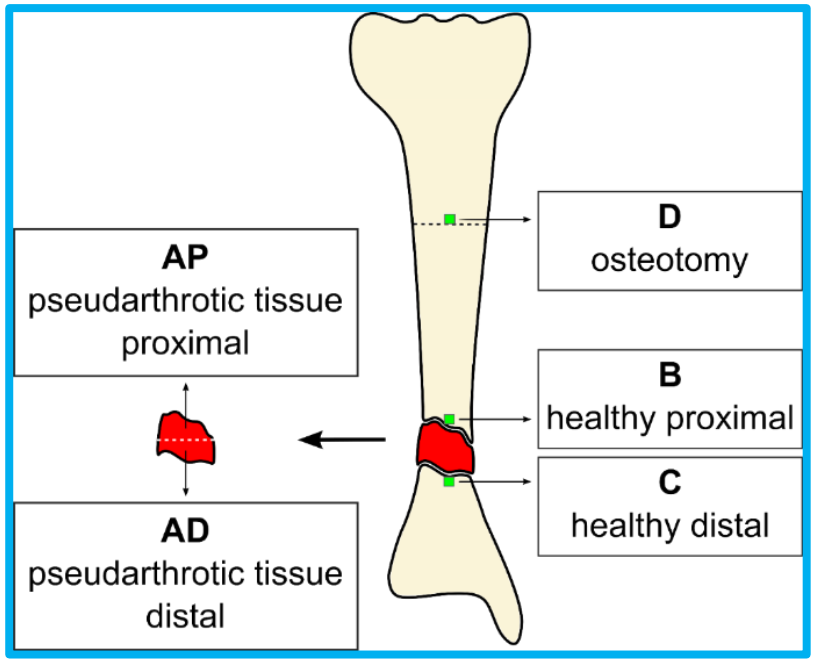
- Melanocyte cultures from CAL macules show bi-allelic inactivation of *NF1* gene
  - Every CAL macule has a different second hit in *NF1*

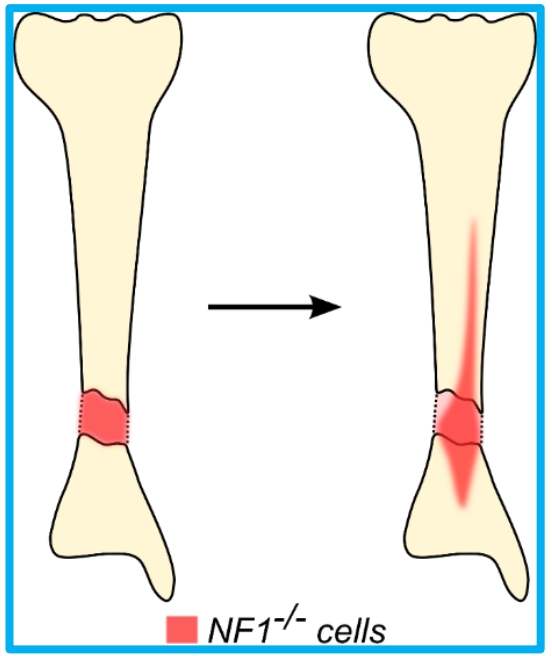


Maertens et al, 2007; De Schepper et al, 2008

Aetiology of pseudarthrosis



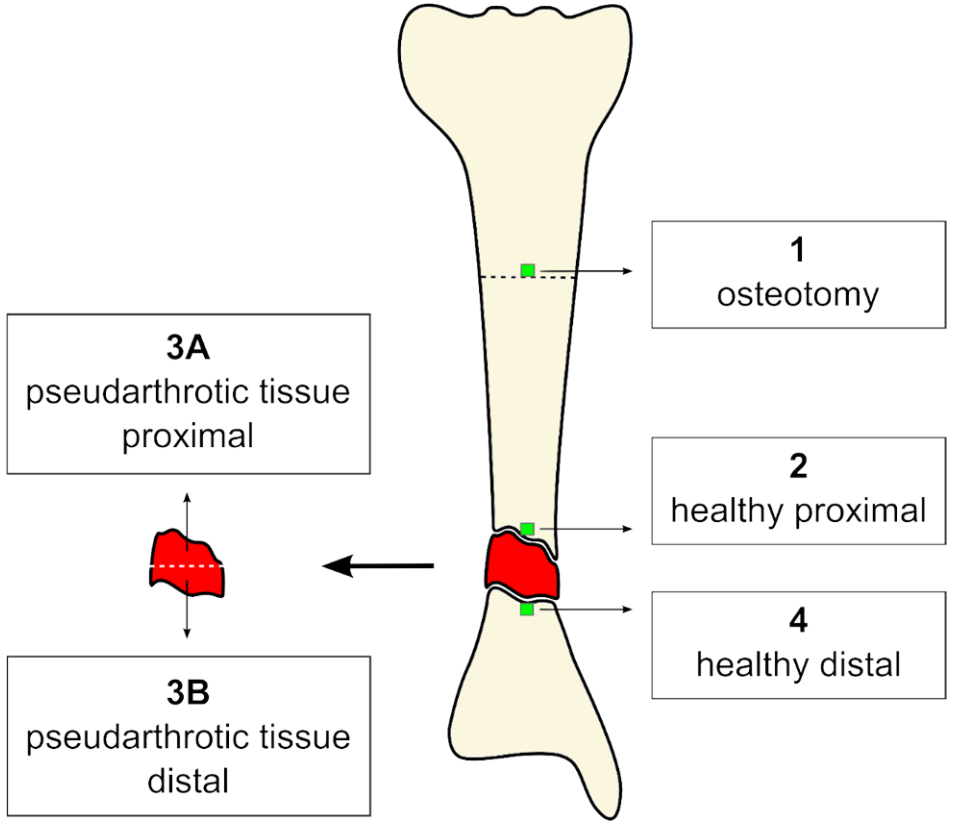




Stevenson et al., Am J Hum Genet, 2006
Lee et al., J Orthop Res, 2012
Sant et al., J Med Genet, 2015
Brekelmans C et al., unpublished

Results of extensive sampling

Tibia F		Tibia G		Radius H	
Sampling	**NGS**	**Sampling**	**NGS**	**Sampling**	**Sanger**
1	32%	1	2%		
2	33%	2	17%	2	76%
3Ai	30%	3A	42%	3Ai	78%
3Aii	7%			3Aii	72%
3Aiii	94%			3Aiii	90%
3Bi	34%	3B	4%	3Bi	74%
3Bii	97%			3Bii	62%
4	77%	4	92%	4	15%



EARLY REPORTS

Early reports

Frequency of choroidal abnormalities in neurofibromatosis type 1

Lancet, 2000

Takaharu Yasunari, Kunihiko Shiraki, Hideji Hattori, Tokuhiko Miki

Parrozzani et al., 2015
Choroidal abnormalities present in 60% of children < 16y
Lisch nodules in 62%

Vagge et al., 2015
Choroidal abnormalities in 69% of children < 16y
Lisch nodules in 48.7%

Viola et al., 2012
Choroidal abnormalities in 71% of children < 16y
Lisch nodules in 43%

OCT machine

Investigative Ophthalmology & Visual Science

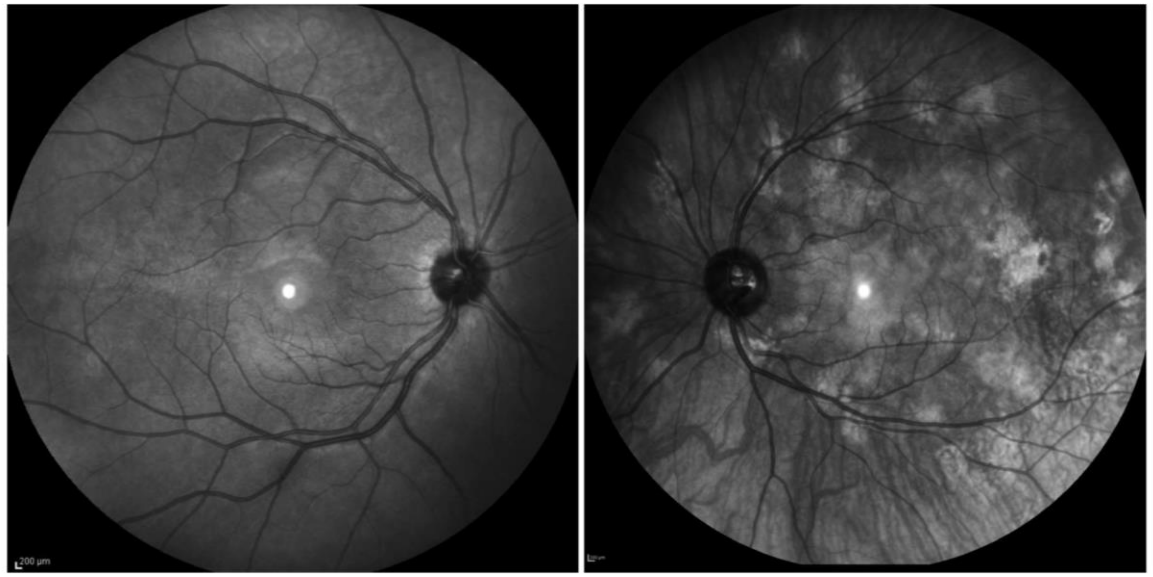


FIGURE. Near-infrared imaging of a 4-year-old boy with NF1 showing no NF1-related choroidal abnormalities in his right eye (*left*). Near-infrared imaging of a 5-year-old boy with NF1 showing several bright NF1-related choroidal abnormalities (*right*).

Parrozzani et al., 2015

140 paediatric patients (0-16y)

Choroidal abnormalities present in 60% of children < 16y

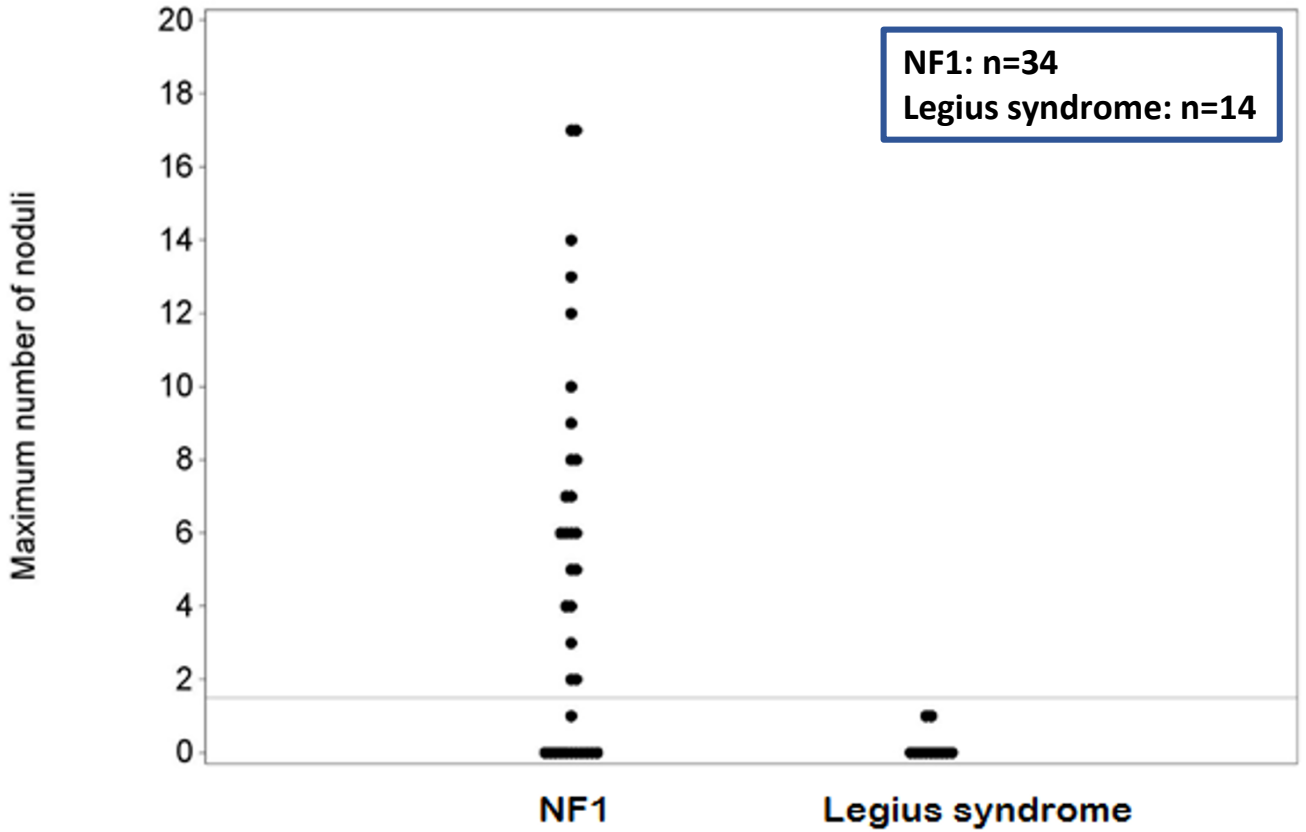
Table 3. Comparison Among Diagnostic Indicators, Rate (95% CI)

	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Café-au-lait spots	98.6 (94.9–99.8)	32.2 (20.6–45.6)	77.5 (70.7–83.4)	90.5 (69.6–98.5)	1.45 (1.22–1.74)	0.04 (0.01–0.18)
Axillary or inguinal freckling	92.9 (87.2–96.5)	100 (93.9–100.0)	100 (97.2–100.0)	85.5 (74.9–92.8)	n.a.	0.07 (0.04–0.13)
Lish nodules	62 (53.0–70.4)	93.3 (81.7–98.5)	96.4 (89.8–99.2)	46.1 (35.6–56.9)	9.3 (3.1–28.0)	0.41 (0.32–0.50)
Neurofibromas	32.9 (25.2–41.3)	98.3 (90.9–99.7)	97.9 (88.9–99.6)	38.2 (30.4–46.4)	19.4 (2.7–137.3)	0.68 (0.61–0.77)
Familiarity	26.3 (19.1–34.5)	81 (68.6–90.1)	76.6 (62.0–87.7)	31.8 (24.4–39.9)	1.39 (0.76–2.53)	0.91 (0.78–1.07)
OPG	20 (13.7–27.6)	98.3 (90.9–99.7)	96.5 (82.2–99.4)	34.1 (27.0–41.8)	11.8 (1.6–84.7)	0.81 (0.74–0.89)
Distinctive osseous lesions	2.14 (0.47–6.14)	100 (93.8–100.0)	100 (30.5–100.0)	29.7 (23.4–36.9)	n.a.	0.98 (0.95–1.00)
NF1-related choroidal abnormalities	60.5 (51.1–69.3)	97.6 (87.1–99.6)	98.6 (92.6–99.8)	46 (35.2–57.0)	24.8 (3.6–172.9)	0.4 (0.32–0.51)

n.a., not applicable; NLR, negative likelihood ratio, (1 − sensitivity)/specificity; NPV, negative predicted value; PLR, positive likelihood ratio, sensitivity/(1 − specificity); PPV, positive predictive value.

Choroidal abnormalities in café-au-lait syndromes: A new differential diagnostic tool.

Cassiman et al, 2016, Clin Genet



Accuracy for predicting NF1 versus Legius Syndrome with cut-off after 1 (≤1 vs ≥2) nodule

Dermatology

Dermatology 2013;226:115–118
DOI: 10.1159/000346643

Anemic Nevus in Neurofibromatosis Type 1

G. Tadini[a, b] M. Brena[a] L. Pezzani[a] C. Gelmetti[a] F. Santagada[a]
M.P. Boldrini[c]

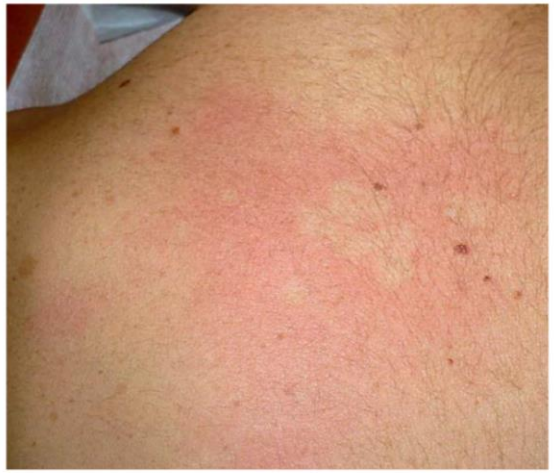


Fig. 1. AN is characterized by pale, sharply bordered and well-defined patches, which are sometimes surrounded by smaller satellite spots.

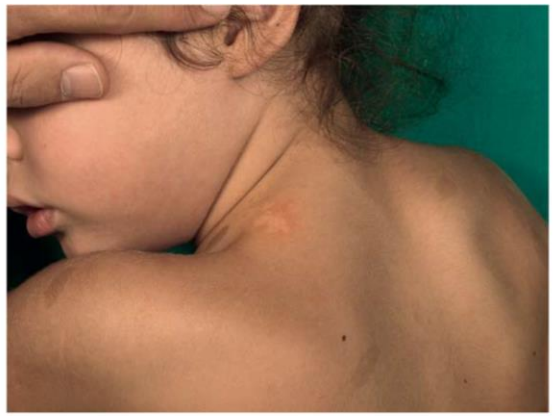
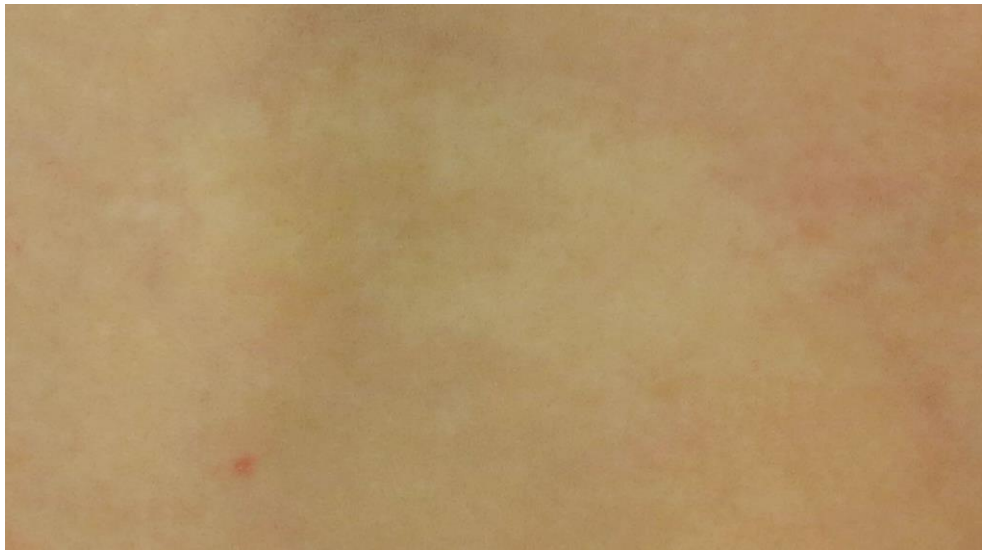


Fig. 3. Image of child with AN symptoms around the neck.

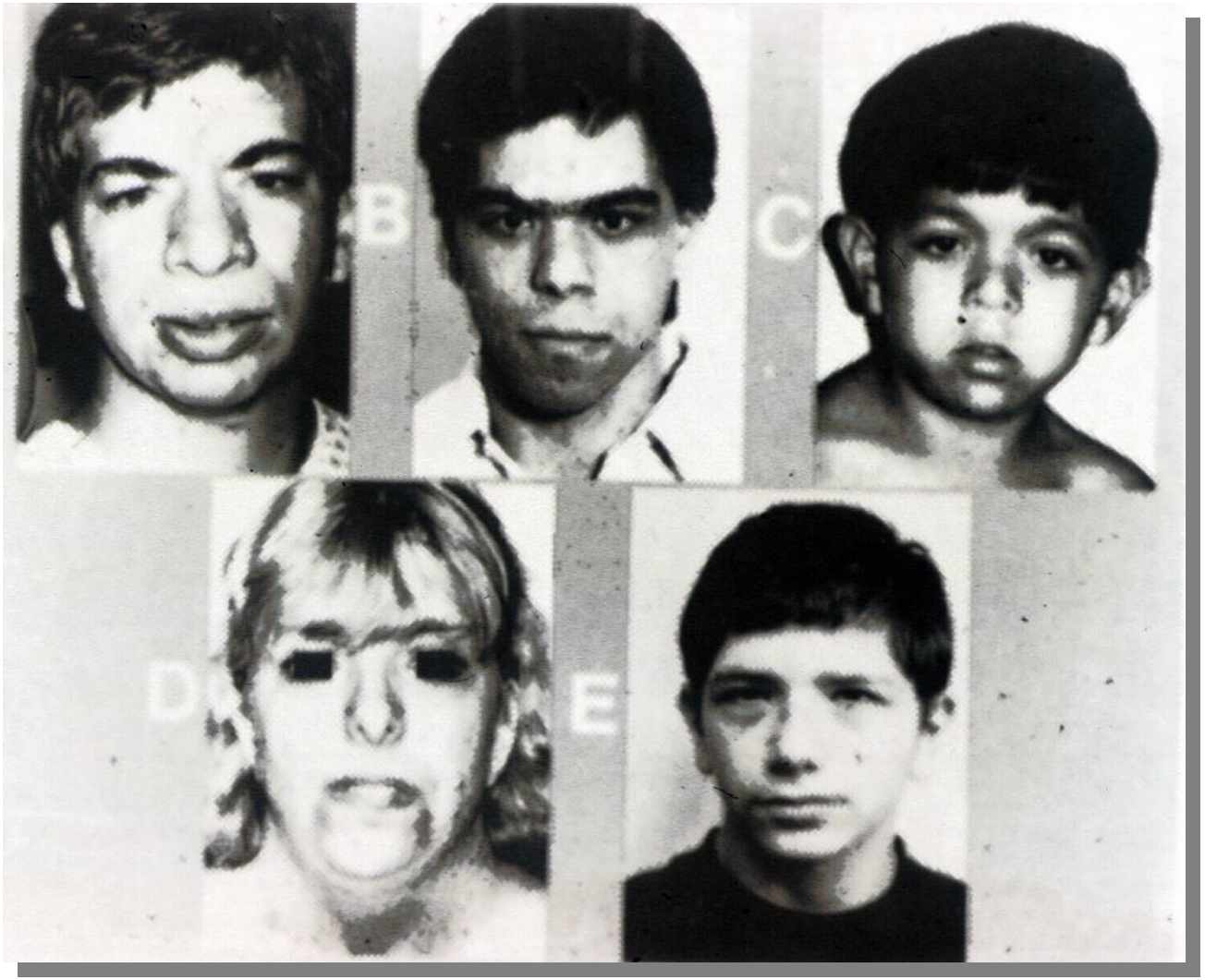
- Naevus anemicus in child with Legius S



Bulteel et al., JAAD Case Rep (2018)

Genotype-Phenotype correlations

- Mostly no genotype-phenotype correlation
- Exceptions
  - **NF1 microdeletion**: more neurofibromas, higher risk for MPNST, lower average IQ, facial dysmorphy, no short stature
  - **Met992del**: no neurofibromas, no OPG, few Lisch nodules, pulmonic stenosis
  - **Arg1809** missenses: no neurofibromas, no OPG, few Lisch nodules, short stature, Noonan phenotype, pulmonic stenosis
  - **AA 844-848** missenses: fewer CAL spots and freckling, more plexiform and spinal neurofibromas, more OPG, more scoliosis, more MPNST



KAYES et al. Deletions spanning the neurofibromatosis I gene: Identification and phenotype of five patients. *Am.J.Hum.Genet.,* 1994, *54*, 424-436.

Am. J. Hum. Genet. 72:1288–1292, 2003

Report

Elevated Risk for MPNST in *NF1* Microdeletion Patients

T. De Raedt,[1] H. Brems,[1] P. Wolkenstein,[3] D. Vidaud,[4] S. Pilotti,[5] F. Perrone,[5] V. Mautner,[6] S. Frahm,[7] R. Sciot,[2] and E. Legius[1]

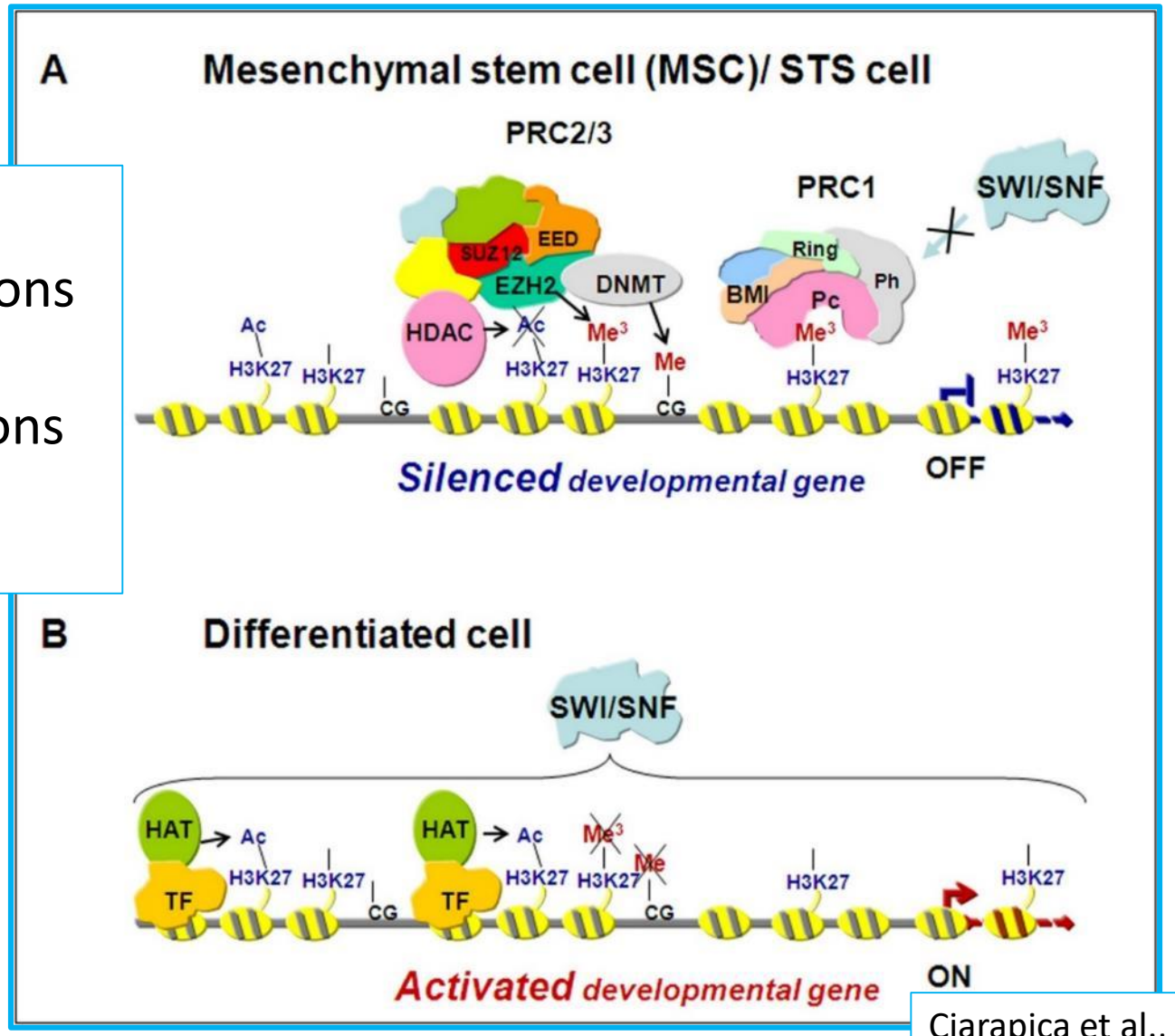
[1]Department of Human Genetics and [2]Department of Pathology, Catholic University Leuven, Leuven, Belgium; [3]Department of Dermatology, Hôpital Henri-Mondor, Creteil, France; [4]Laboratoire de Génétique Moléculaire, Upres, France; [5]Unit of Experimental Molecular Pathology, Department of Pathology, Istituto per lo Studio e la Cura dei Tumori, Milan; [6]Department of Neurology, Klinikum Nord, and [7]Laboratory of Brain Tumor Biology, Department of Neurosurgery, University Hospital Eppendorf, Hamburg

An *NF1* microdeletion is the single most commonly reported mutation in individuals with neurofibromatosis type 1 (NF1). Individuals with an *NF1* microdeletion have, as a group, more neurofibromas at a younger age than the group of all individuals with NF1. We report that *NF1* microdeletion individuals additionally have a substantially higher lifetime risk for the development of malignant peripheral nerve sheath tumors than individuals with NF1 who do not have an *NF1* microdeletion. This should be taken into account in the medical follow-up of individuals with an *NF1* microdeletion.

SUZ12 is the microdeletion gene responsible for the increased MPNST risk!

- 51 MPNSTs
  - Array CGH: homozygous deletions of ***SUZ12***
  - Exome analysis: ***SUZ12*** mutations are recurring

SUZ12 is a member of PRC2: Polycomb repressor complex 2



Ciarapica et al., 2011

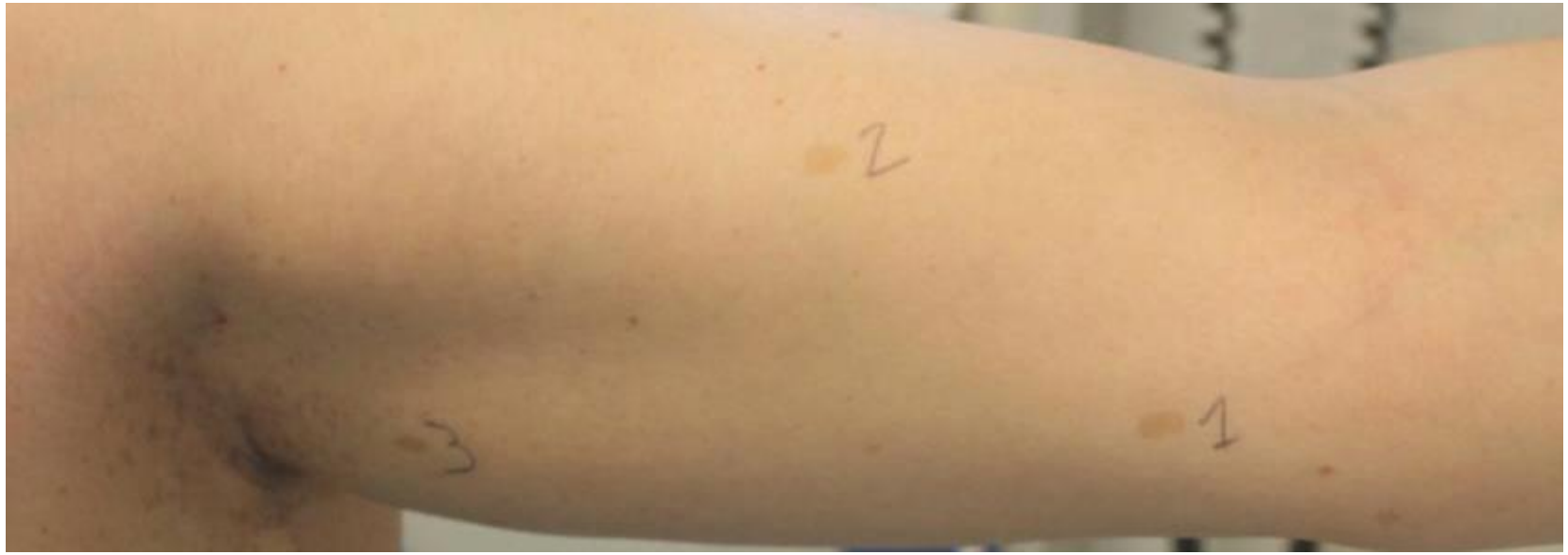
LETTER

doi:10.1038/nature13561

PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies

Thomas De Raedt[1,2,3], Eline Beert[4]*†, Eric Pasmant[5,6]*, Armelle Luscan[5,6], Hilde Brems[4], Nicolas Ortonne[5,6], Kristian Helin[7,8,9], Jason L. Hornick[10], Victor Mautner[11], Hildegard Kehrer-Sawatzki[12], Wade Clapp[13], James Bradner[2,14], Michel Vidaud[5,6], Meena Upadhyaya[15], Eric Legius[4,16] & Karen Cichowski[1,2,3]

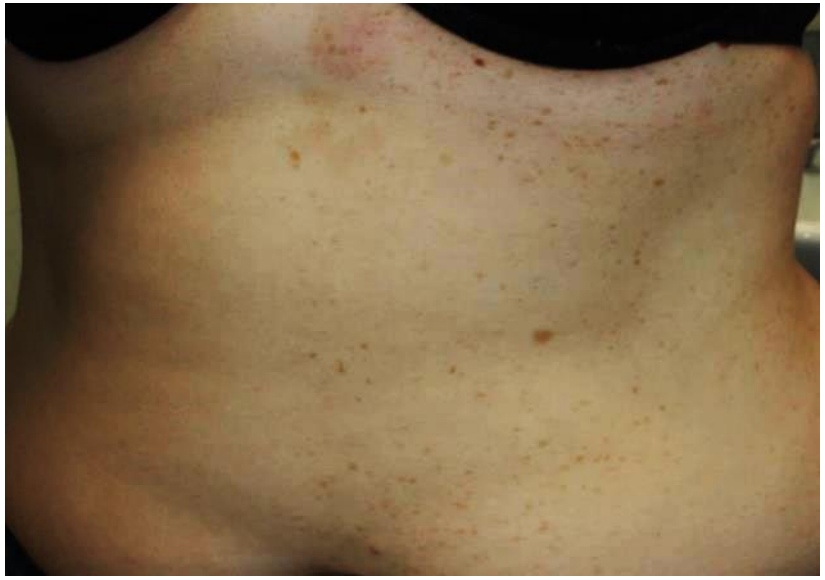
Mosaic manifestation



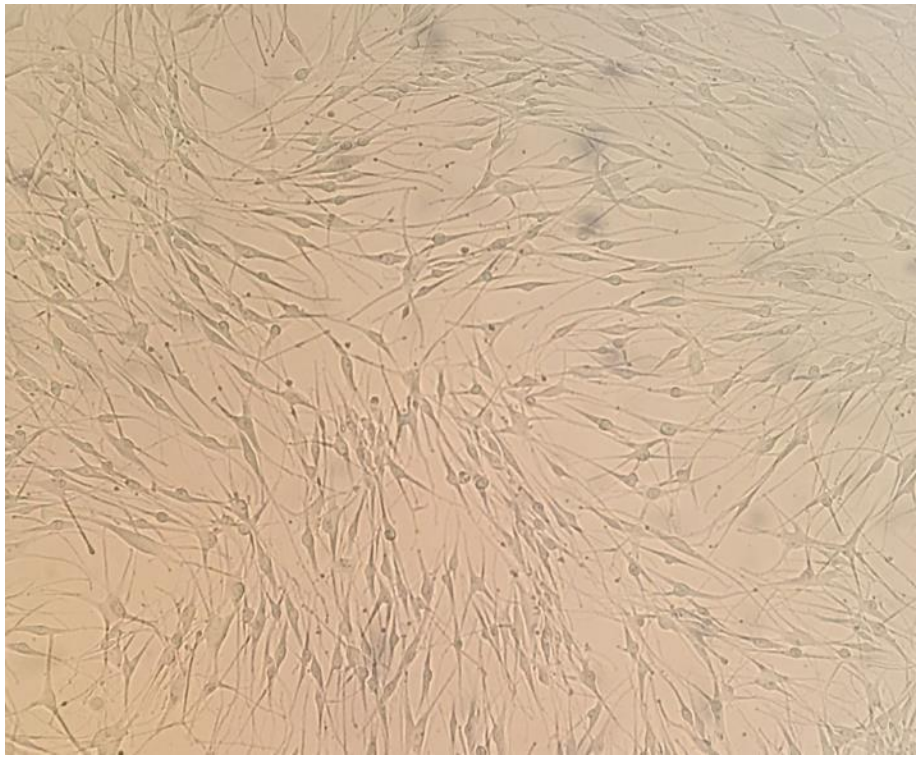
Segmental distribution of café-au-lait spots

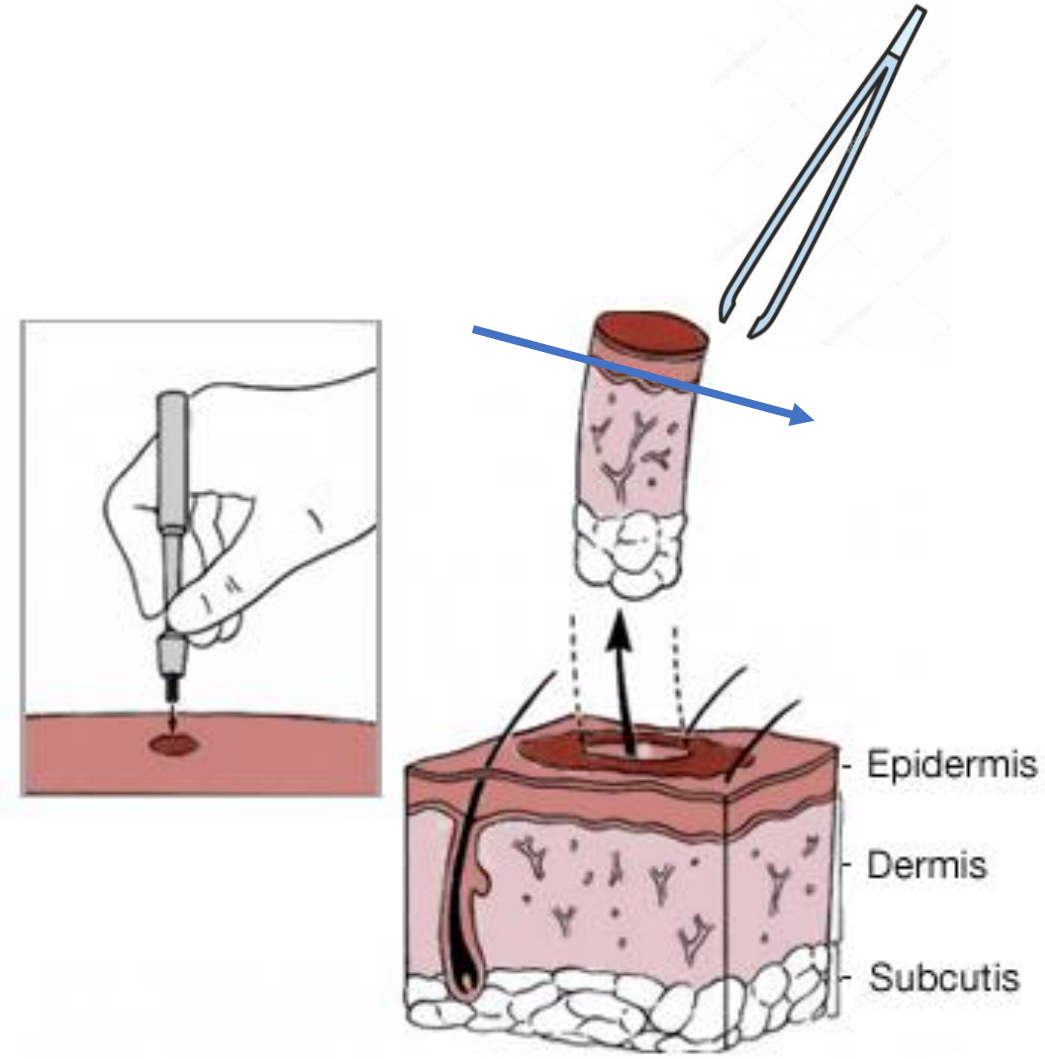
Only on left side of midline

Freckling only in left axilla



Melanocytes





MNF1: mutation types detected

- Mosaic *NF1* mutation: n=28
  - 7 mutations detectable in blood, 21 only in affected tissue
  - Multi-exon deletion, whole gene deletion, insertional translocation: 16
  - Small in/del; base substitution: 12

- Second hit mutation *NF1*: n=24
  - Multi-exon or whole gene deletion or copy neutral LOH (first hit deletion): 12
  - Small in/del; base substitution: 12

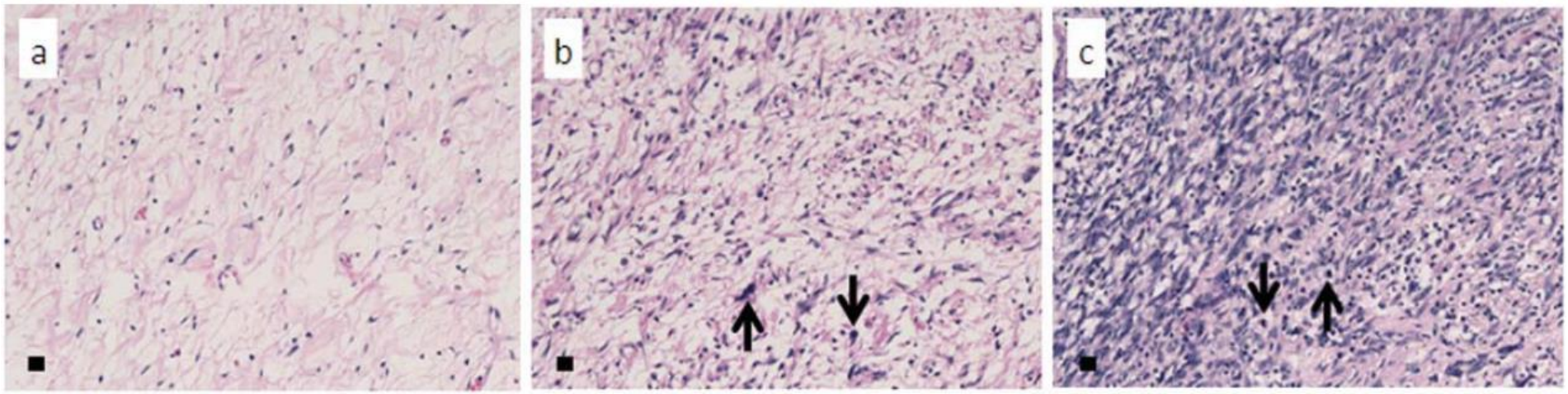
Mosaic NF1

- Mosaic NF1 can be associated with complications
  - Epilepsy, optic pathway glioma, learning disabilities, …
- Potential risk for germline transmission
  - Mosaic *NF1* mutation needed if prenatal testing is requested
- Different spectrum of mutations:
  - Multi-exon deletions and whole gene deletions in 50%
  - Large deletions are not detected by NGS/Sanger sequencing at low level mosaicism
  - Need for specific culture of melanocytes and Schwann cells to detect mosaic *NF1* mutation/large deletions

GENES, CHROMOSOMES & CANCER 50:1021–1032 (2011)

Atypical Neurofibromas in Neurofibromatosis Type 1 are Premalignant Tumors

Eline Beert,[1] Hilde Brems,[1] Bruno Daniëls,[2] Ivo De Wever,[3] Frank Van Calenbergh,[4] Joseph Schoenaers,[5] Maria Debiec-Rychter,[1] Olivier Gevaert,[6] Thomas De Raedt,[7] Annick Van Den Bruel,[8] Thomy de Ravel,[1] Karen Cichowski,[7] Lan Kluwe,[9,10] Victor Mautner,[9] Raf Sciot,[11] and Eric Legius[1]*



aCGH

- typical benign neurofibromas
  - **no recurrent copy number alterations** (CNAs)
- atypical neurofibromas
  - **1 significantly recurrent deletion: 9p**
  - minimal overlapping region (MOR) of 160 kb: *CDKN2A/B*
  - other MORs at 9p (less frequent:5-6/16)
  - Few other CNAs in 13/16 tumors
- MPNSTs
  - **high number of recurrent CNAs**
  - 16/23 (70%): deletion *CDKN2A* (12/23 homozygous)

Neuro-Oncology
20(6), 818–825, 2018 | doi:10.1093/neuonc/noy013 | Advance Access date 2 February 2018

The characteristics of 76 atypical neurofibromas as precursors to neurofibromatosis 1 associated malignant peripheral nerve sheath tumors

Christine S. Higham, Eva Dombi, Aljosja Rogiers, Sucharita Bhaumik, Steven Pans, Steve E. J. Connor, Markku Miettinen, Raf Sciot, Roberto Tirabosco, Hilde Brems, Andrea Baldwin, Eric Legius,* Brigitte C. Widemann,* and Rosalie E. Ferner*

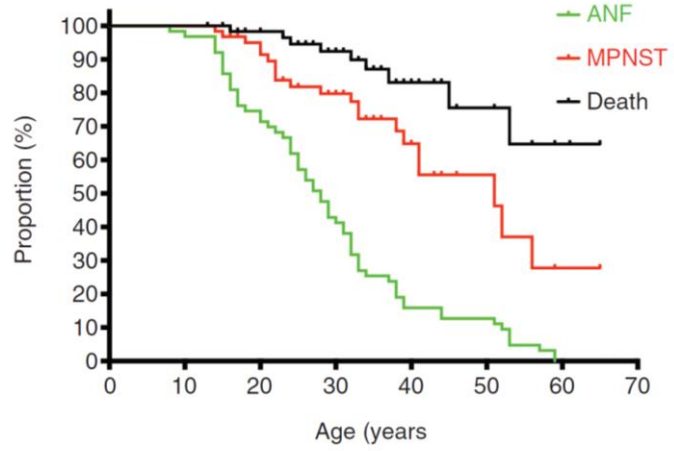


Fig. 2 Kaplan–Meier curve: proportion of patients with disease manifestations: age in years at first ANF, first MPNST, and death. All MPNST were included: MPNST prior to diagnosis of ANF or after diagnosis of ANF, whether transformed or developed in a different location.

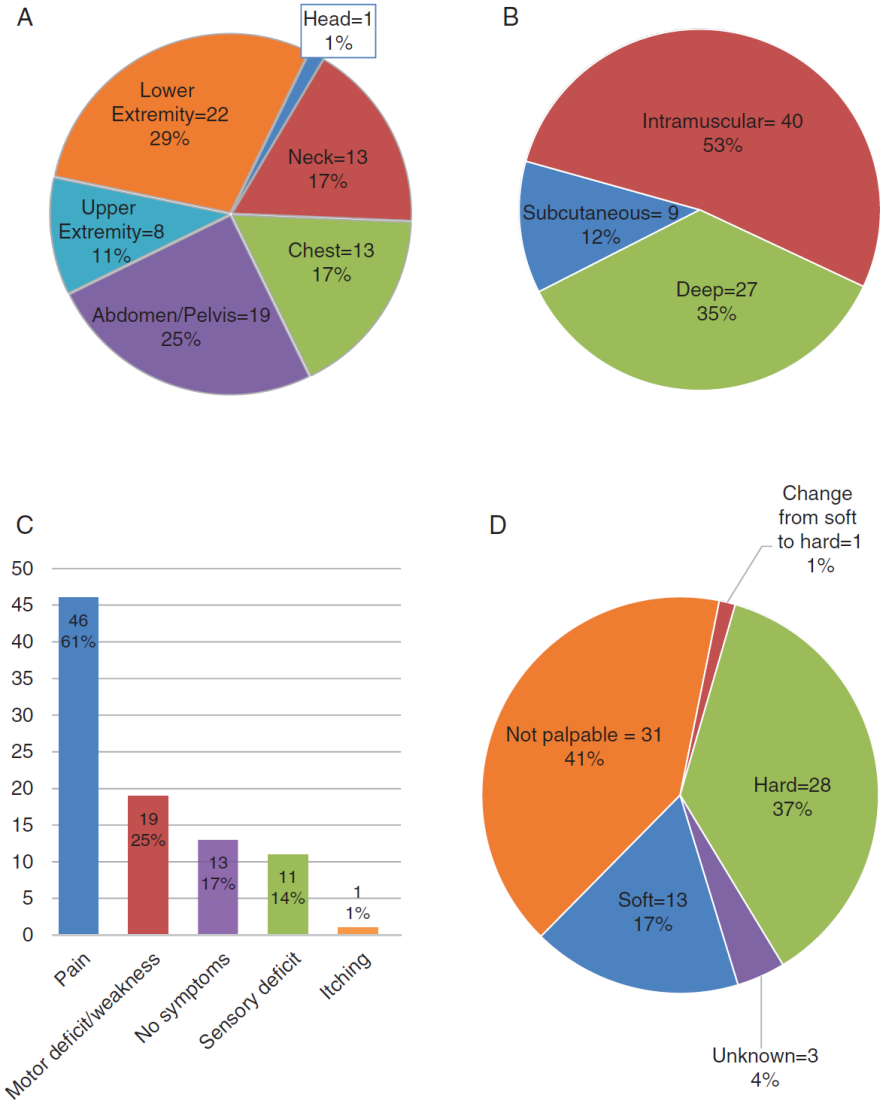
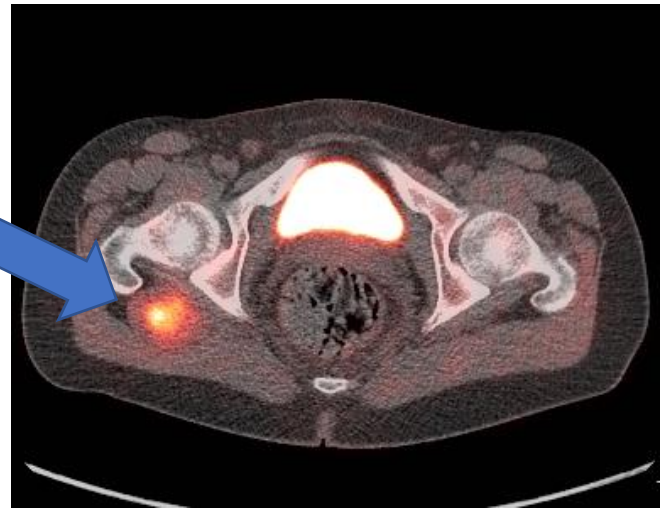


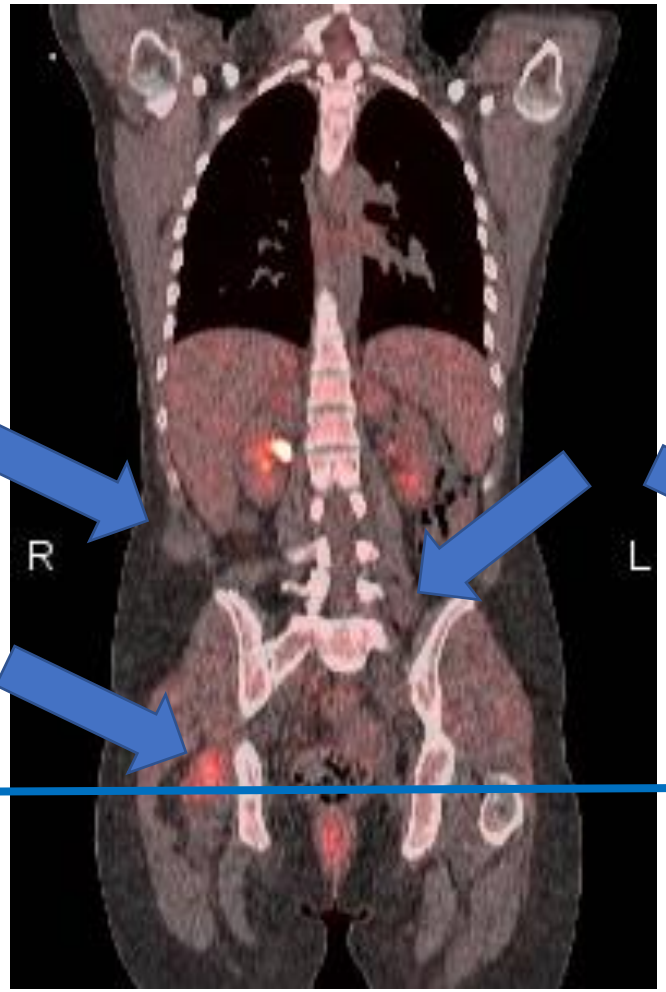
Fig. 1 (A) Location of atypical neurofibromas. (B) Location of atypical neurofibromas in fascial plane. (C) Symptoms related to atypical neurofibromas. (D) Texture on palpation of atypical neurofibromas.

FDG-PET: atypical and benign neurofibromas

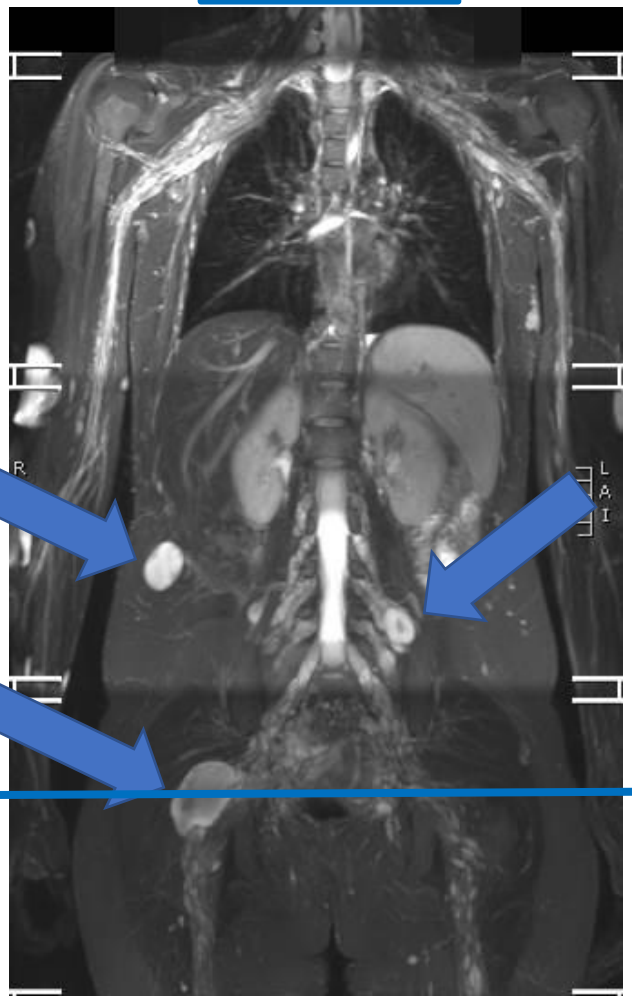
PET-CT



PET-CT



WB-MRI



PET-CT: positron emission tomography - CT scan

Factors associated with increased MPNST risk

- *NF1* microdeletion, *NF1* missense mutations AA 844-848
- High total volume of internal neurofibromas (full body MRI)
  - Nguyen et al., 2014
  - Tucker et al., 2005 (hard subcutaneous neurofibromas)
- Atypical neurofibromas (discrete nodular lesions, ANNUBP)
- Neurofibromatous neuropathy (rare)
- Family history of MPNST (rare)
- Field of previous radiotherapy (rare)

Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 1

D. Gareth R. Evans[1,2], Hector Salvador[3], Vivian Y. Chang[4,5,6], Ayelet Erez[7], Stephan D. Voss[8], Kami Wolfe Schneider[9], Hamish S. Scott[10], Sharon E. Plon[11], and Uri Tabori[12,13]

Table 3. Summary of recommendations for childhood management

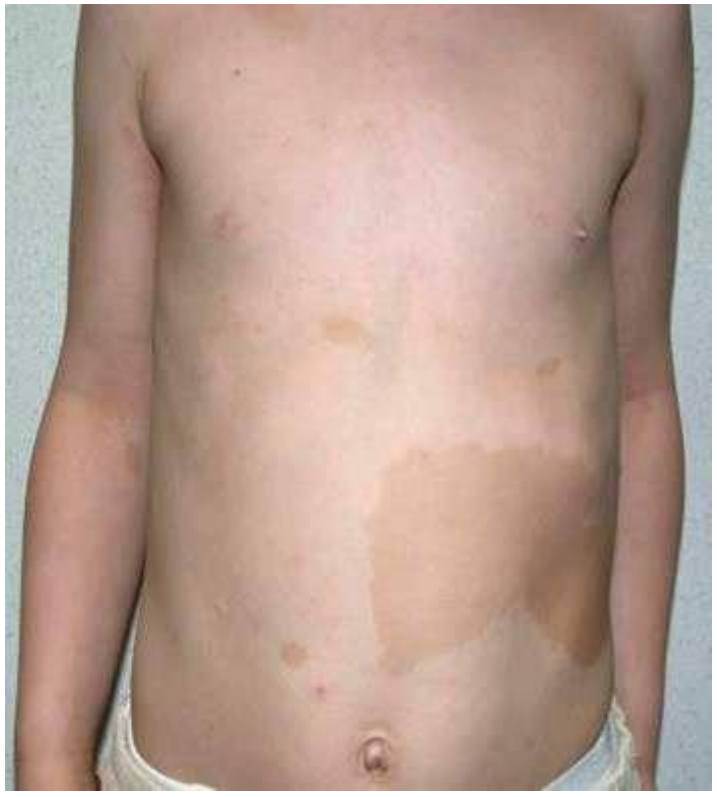
1. Genetic testing	Children considered at risk of NF1 especially with 6+ CAL macules or diagnosed with NIH criteria should ideally have genetic testing of the *NF1* gene with an RNA-based approach and testing of SPRED1 if pigmentary features only
2. Genetic testing	Those testing negative should be considered for a panel of genes including *GNAS, MLH1, MSH2, MSH6, NF2, PMS2, PTPN11, SOS1*, and *SPRED1* (if not already tested)
3. General	Annual history and physical exam (including skin and neurologic exam and also blood pressure, height, weight, and pubertal development)
Tumor surveillance	
4. OPG	Children with NF1 should have 6–12 monthly ophthalmic assessments from birth to 8 years. One baseline assessment of color vision and visual fields should be undertaken when the child is developmentally able.
5. MPNST	Assess with history and clinical examination annually for typical signs of MPNST: any nondermal neurofibroma with rapid growth, loss of neurologic function, or increasing pain or change in consistency
6. JMML	Assess for risk of JMML in NF1 in children with juvenile xanthogranulomas
7. Internal burden	A baseline whole-body MRI should be considered between ages 16 and 20 years to assess internal tumor burden to determine adult follow-up regimen
8. Routine MRI	MRI surveillance is not currently recommended unless symptomatic or with an already diagnosed tumor. Specific biochemical or imaging surveillance for tumors with absolute risks in childhood below 1% is not recommended such as for pheochromocytoma, neuroendocrine tumors, MPNST, or non-optic glioma.

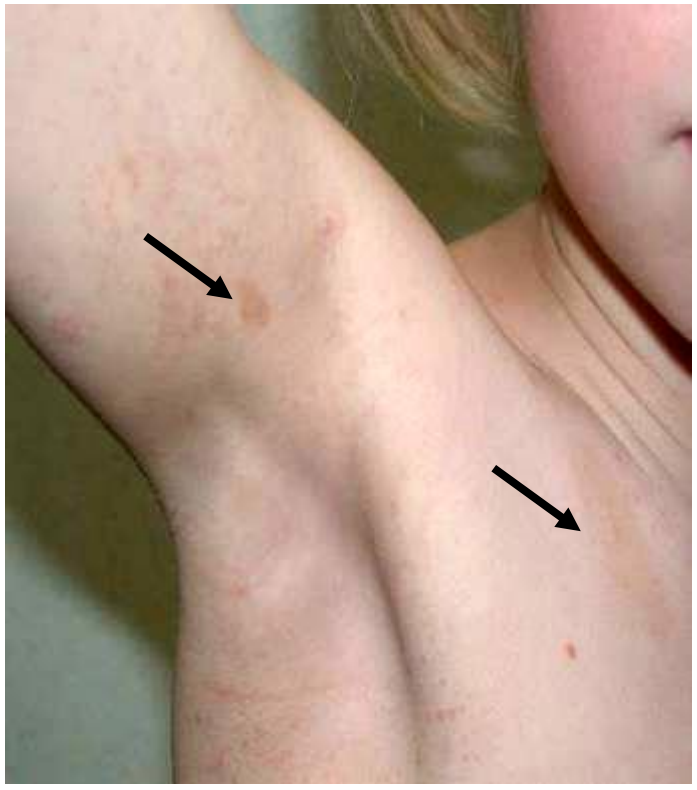
Abbreviation: JMML, juvenile myelomonocytic leukemia.

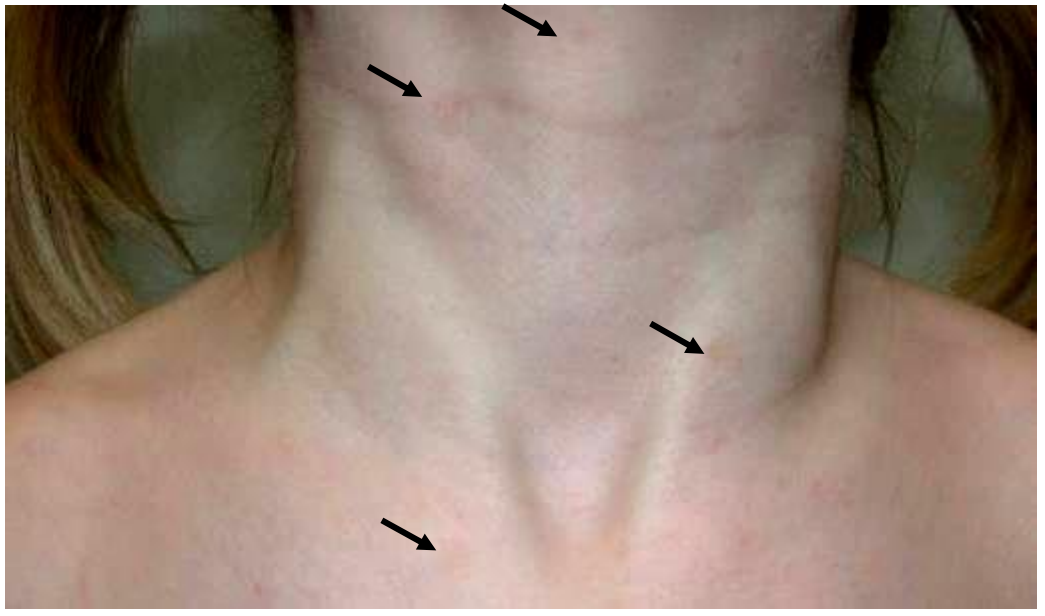
Surveillance in adults

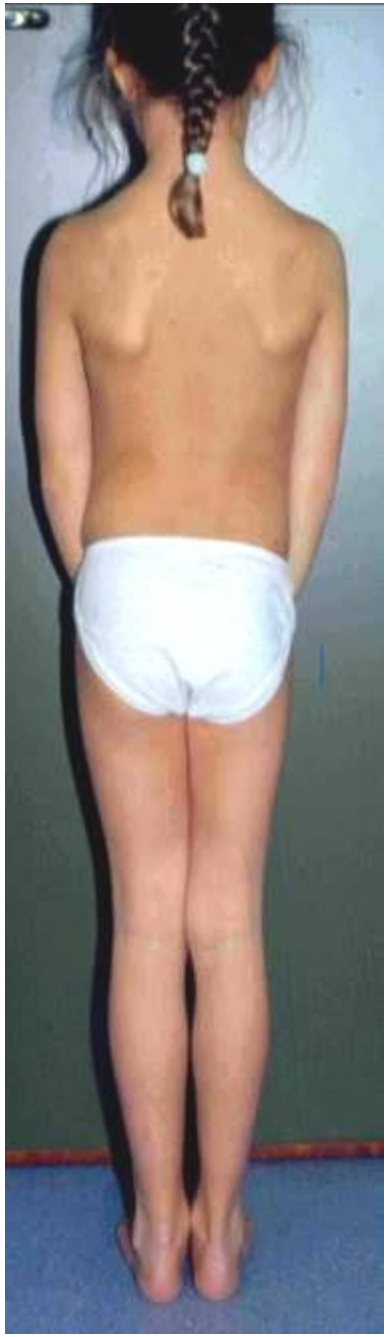
- Cutaneous neurofibromas
- Plexiform neurofibromas
- Atypical neurofibromas and MPNST
- Brain tumours
- Gastrointestinal stromal tumours
- Pheochromocytomas
- Breast cancer in women (30-50y)
- Glomus tumors of the digits
- Arterial hypertension
- Skeletal problems
- Fatigue, depression, …

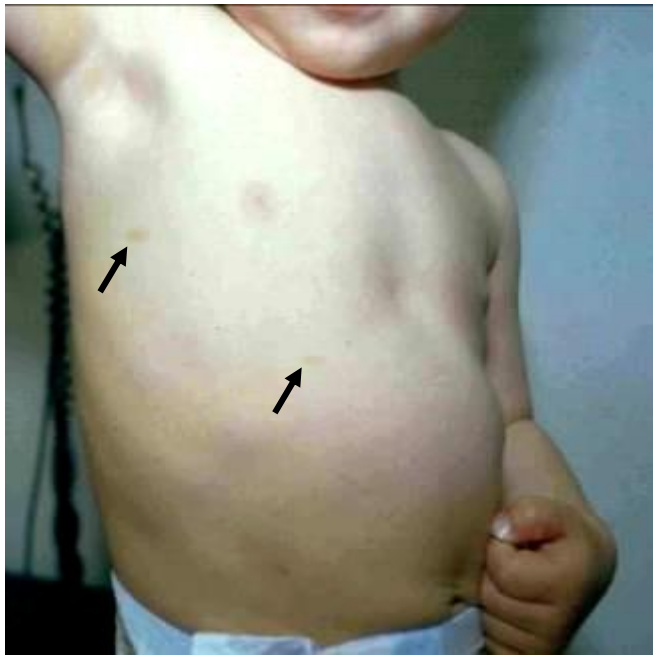
NF1 lookalikes

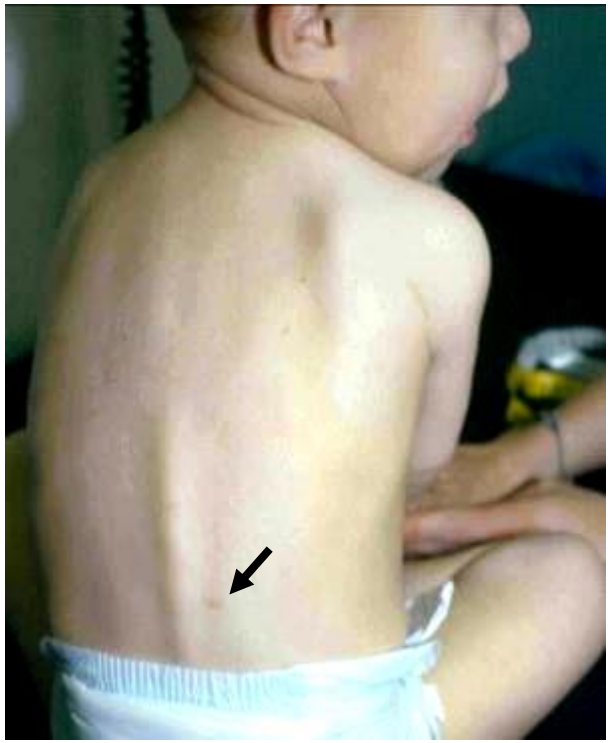


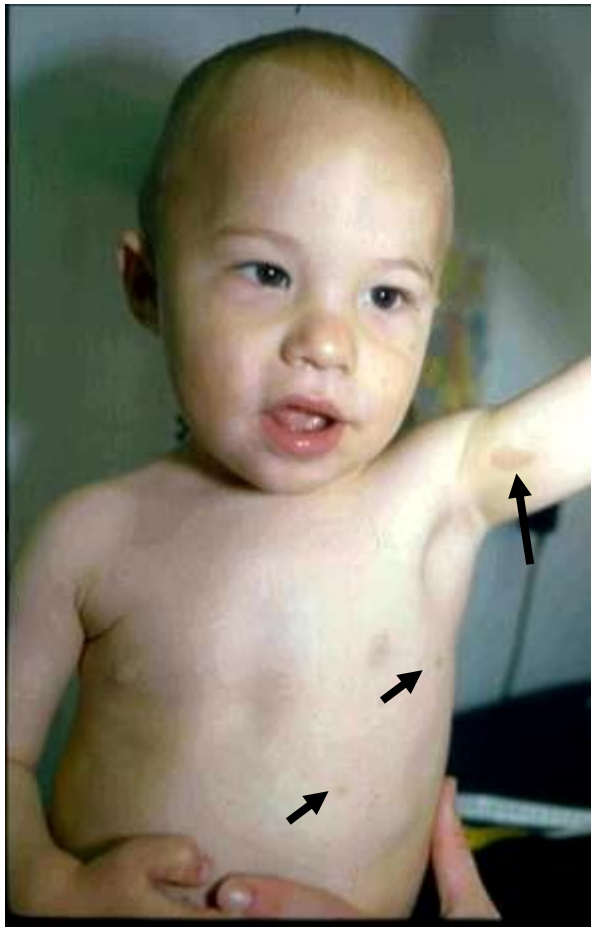








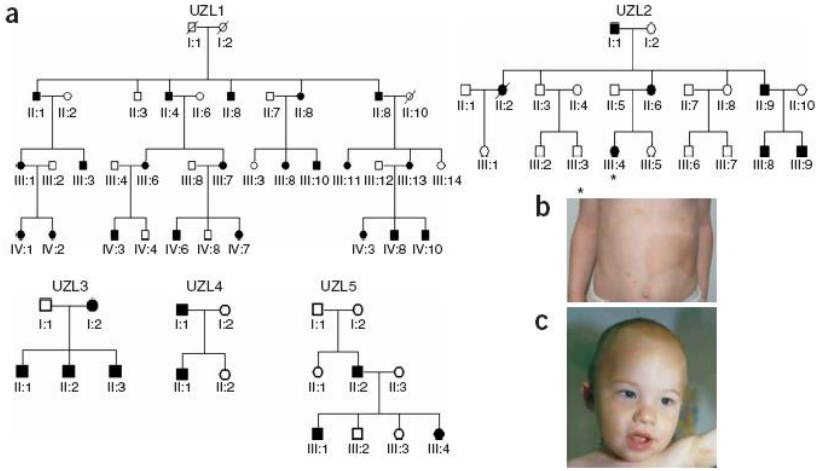




nature genetics

Germline loss-of-function mutations in *SPRED1* cause a neurofibromatosis 1–like phenotype

Hilde Brems[1,9], Magdalena Chmara[1,2,9], Mourad Sahbatou[3,9], Ellen Denayer[1], Koji Taniguchi[4], Reiko Kato[4], Riet Somers[1,5], Ludwine Messiaen[6], Sofie De Schepper[7], Jean-Pierre Fryns[1], Jan Cools[1,5], Peter Marynen[1,5], Gilles Thomas[3,8], Akihiko Yoshimura[4] & Eric Legius[1]



Original article

EDITOR'S CHOICE

SPRED1 mutations (Legius syndrome): another clinically useful genotype for dissecting the neurofibromatosis type 1 phenotype

G Spurlock,[1] E Bennett,[1] N Chuzhanova,[2] N Thomas,[1] H-Ping Jim,[1] L Side,[3] S Davies,[1] E Haan,[4] B Kerr,[5] S M Huson,[5] M Upadhyaya[1]

Clinical and Mutational Spectrum of Neurofibromatosis Type 1–like Syndrome

Ludwine Messiaen, PhD
Suxia Yao, MD
Hilde Brems, MS
Tom Callens, BSc
Achara Sathienkijkanchai, MD
Ellen Denayer, MD
Emily Spencer, BSc
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Mira Irons, MD
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Cynthia Lim, MS
Marie McDonald, MD
Vinodh Narayanan, MD
Amy Pearn, MS
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Berkley Powell, MD
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Annabel Parret, PhD
Bruce Korf, MD, PhD
Eric Legius, MD, PhD

Context Autosomal dominant inactivating sprouty-related EVH1 domain–containing protein 1 (*SPRED1*) mutations have recently been described in individuals presenting mainly with café au lait macules (CALMs), axillary freckling, and macrocephaly. The extent of the clinical spectrum of this new disorder needs further delineation.

Objective To determine the frequency, mutational spectrum, and phenotype of neurofibromatosis type 1–like syndrome (NFLS) in a large cohort of patients.

Design, Setting, and Participants In a cross-sectional study, 22 unrelated probands carrying a *SPRED1* loss-of-function (LOF) mutation identified through clinical testing participated with their families in a genotype-phenotype study (2007-2008). In a second cross-sectional study, 1318 unrelated anonymous samples collected in 2003-2007 from patients with a broad range of signs typically found in neurofibromatosis type 1 (NF1) but no detectable *NF1* germline mutation underwent *SPRED1* mutation analysis.

Main Outcome Measures Comparison of aggregated clinical features in patients with or without a *SPRED1* or *NF1* mutation. Functional assays were used to evaluate the pathogenicity of missense mutations.

Results Among 40 *SPRED1* LOF-positive individuals from the clinical cohort, 20 (50%; 95% confidence interval [CI], 34%-66%) fulfilled National Institutes of Health (NIH) NF1 diagnostic criteria based on the presence of more than 5 CALMs with or without freckling or an NF1-compatible family history. None of the 40 *SPRED1* LOF-positive individuals (0%; 95% CI, 0%-7%) had discrete cutaneous or plexiform neurofibromas, typical NF1 osseous lesions, or symptomatic optic pathway gliomas. In the anonymous cohort of 1318 individuals, 34 different *SPRED1* mutations in 43 probands were identified: 26 pathogenic mutations in 33 probands and 8 probable nonpathogenic missense or silent mutations in 10 probands. Of 94 probands with familial CALMs with or without freckling and no other NF1 features, 69 (73%; 95% CI, 63%-80%) had an *NF1* mutation and 18 (19%; 959 CI, 12%-29%) had a pathogenic *SPRED1* mutation. In the anonymous cohort, 1.99% (95% CI, 1.2%-2.9%) of individuals with the clinical diagnosis of NF1 according to the NIH criteria had NFLS.

Conclusions A high *SPRED1* mutation detection rate was found in *NF1* mutation–negative families with an autosomal dominant phenotype of CALMs with or without freckling and no other NF1 features. Among individuals in this study, NFLS was not associated with the peripheral and central nervous system tumors seen in NF1.

JAMA. 2009;302(19):2111-2118 www.jama.com

See also p 2150 and Patient P

EDITORIAL

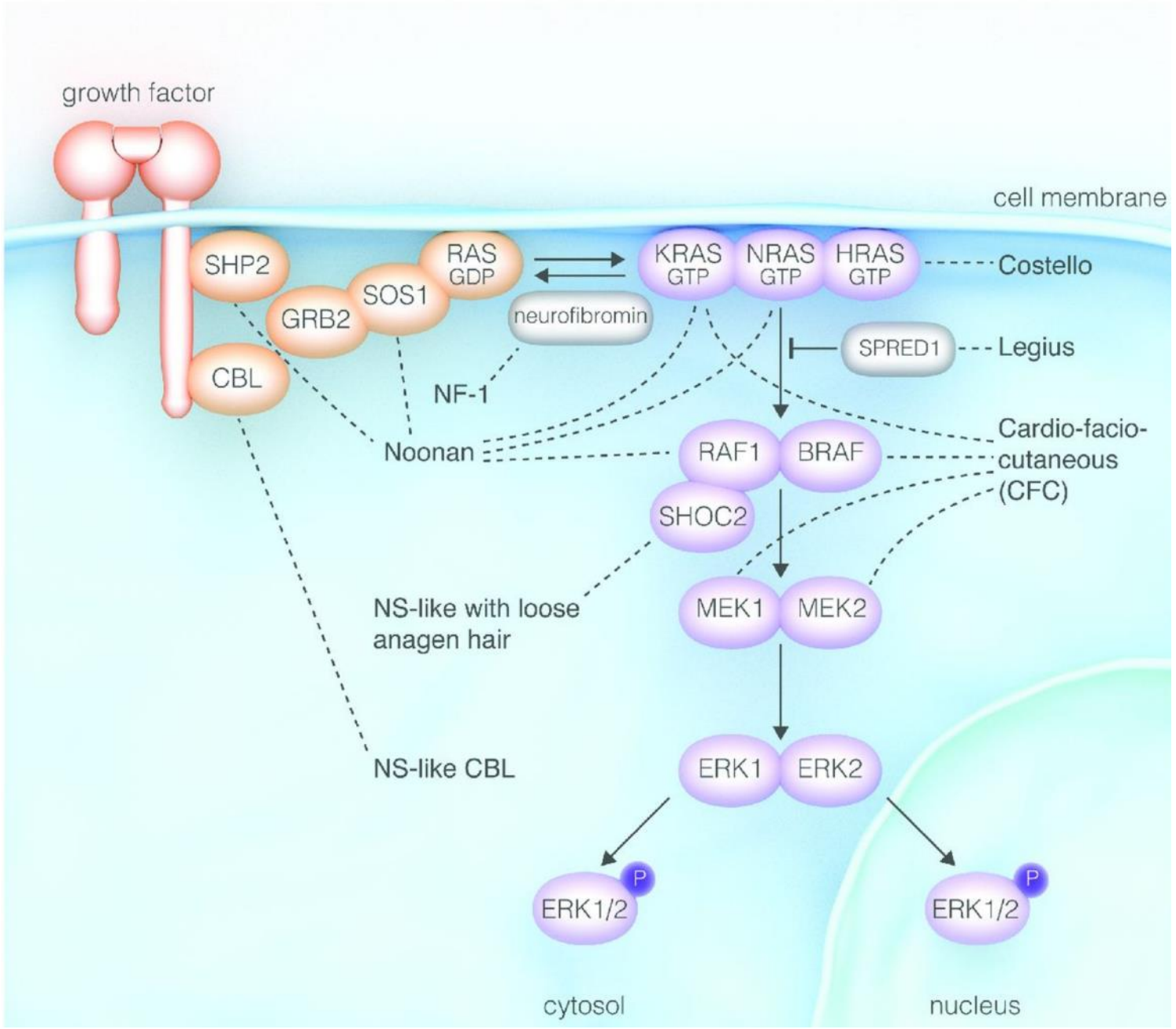
Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Pigmentary Findings in Neurofibromatosis Type 1–like Syndrome (Legius Syndrome)

Potential Diagnostic Dilemmas

David Stevenson, MD
David Viskochil, MD, PhD

activated protein kinase (MAPK) signal transduction pathway in cellular growth and differentiation. Pasmant et al[6] theorized that individuals with Legius syndrome are pre-



Charlotte M. Niemeyer, Haematologica, 2014, 99: 1653-1662.

Clinical features of Legius syndrome

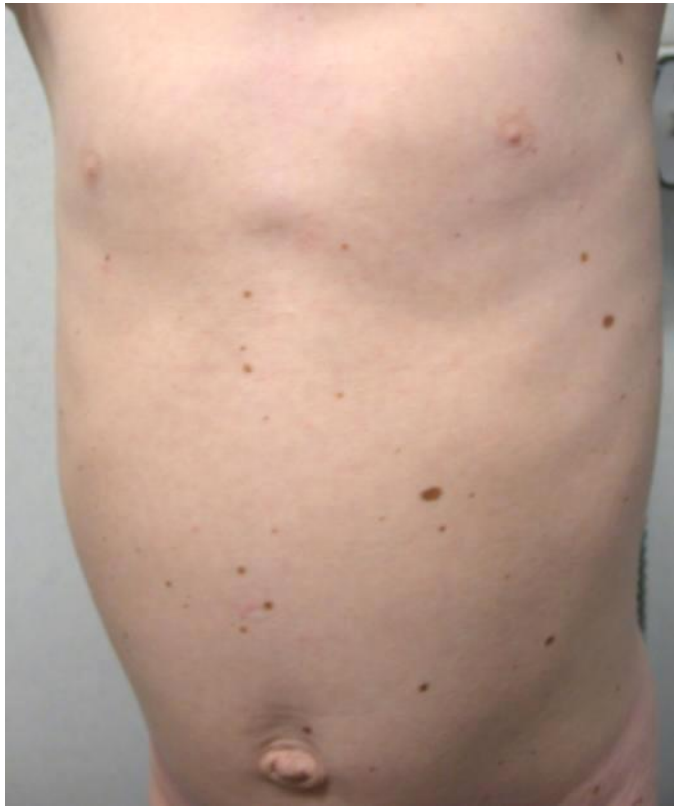
- Café-au-lait spots, with or without freckling
- Macrocephaly
- Noonan-like facial features
- Lipomas in adults
- Less learning problems, ADHD, ASD

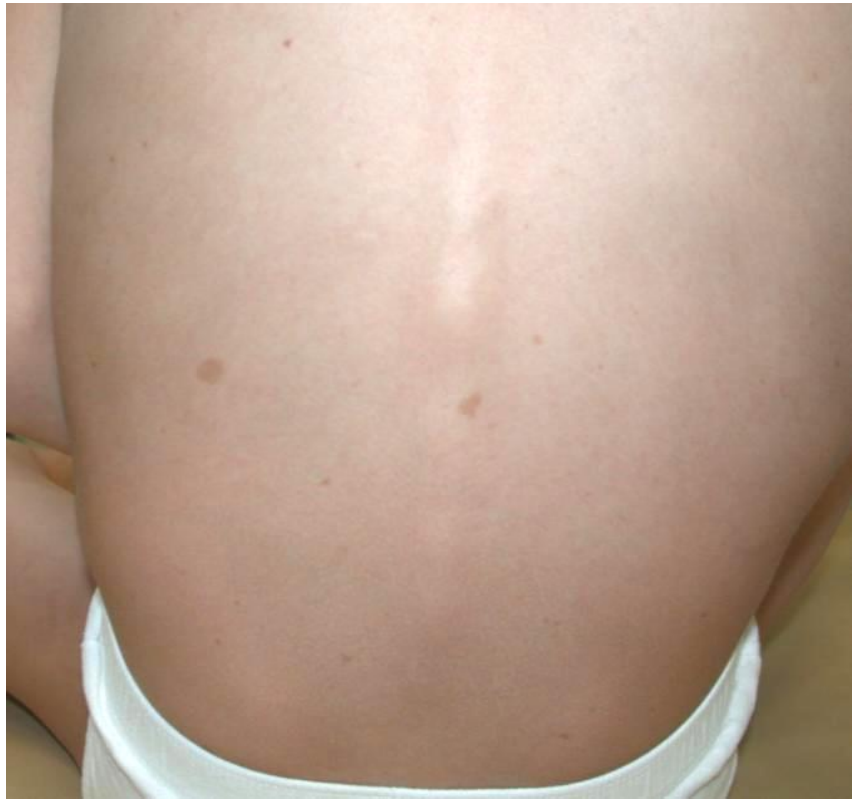
- NO NF1-associated tumours

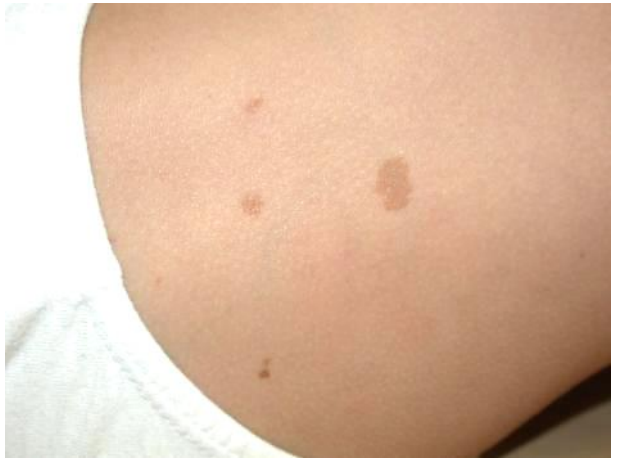
- Important news for parents of a child with multiple CAL spots
- 3-4% of children in follow-up at a multidisciplinary NF clinic

Noonan syndrome with multiple lentigines

PTPN11 and RAF1

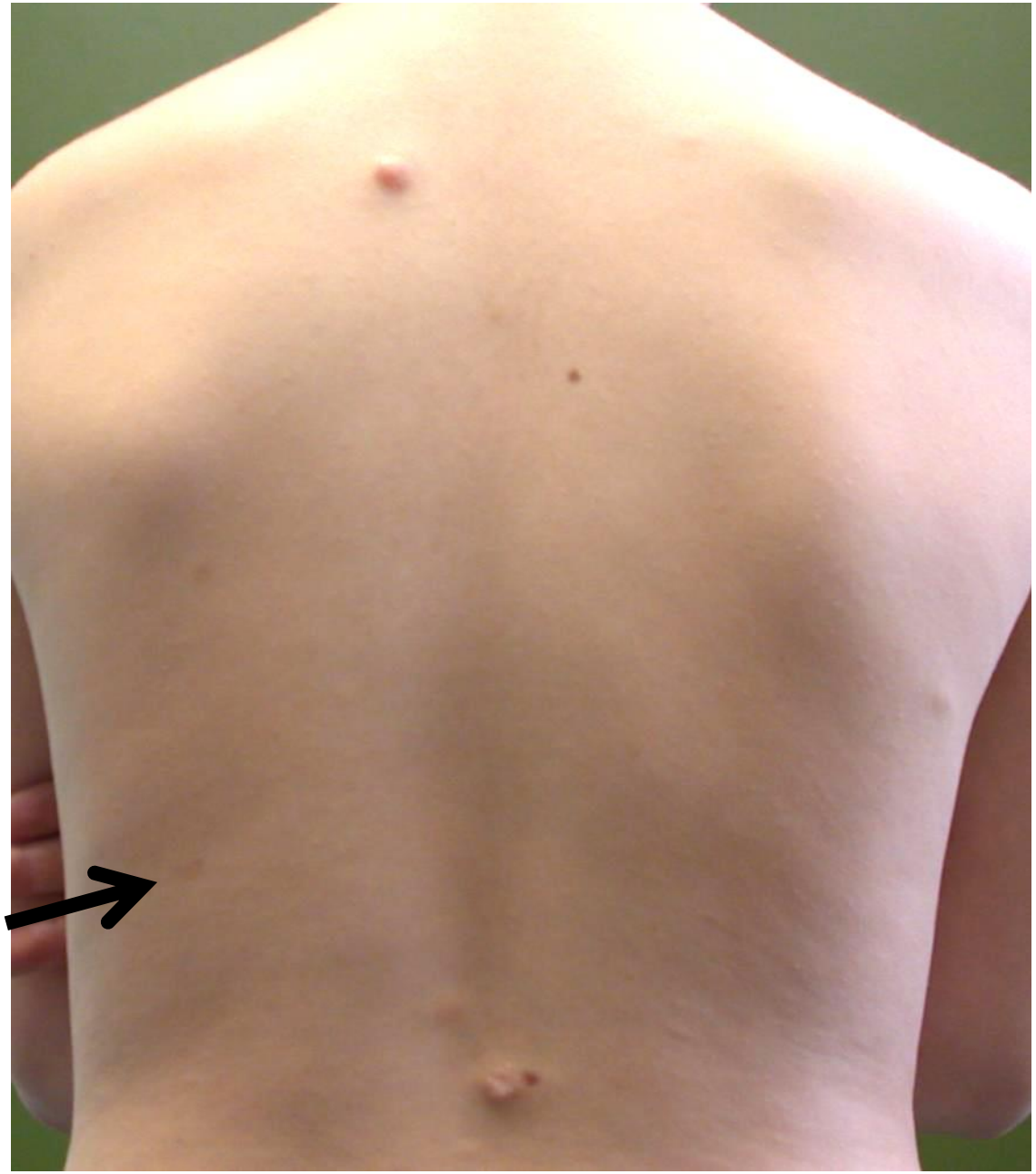


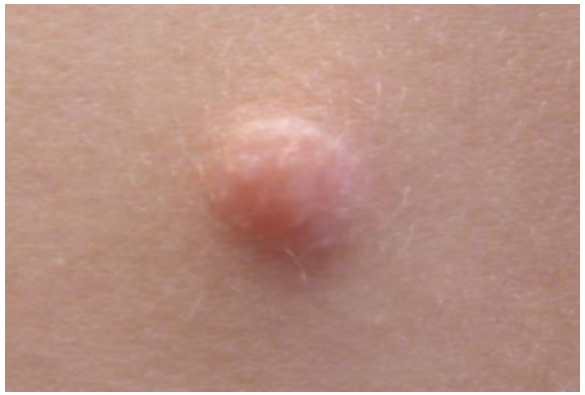


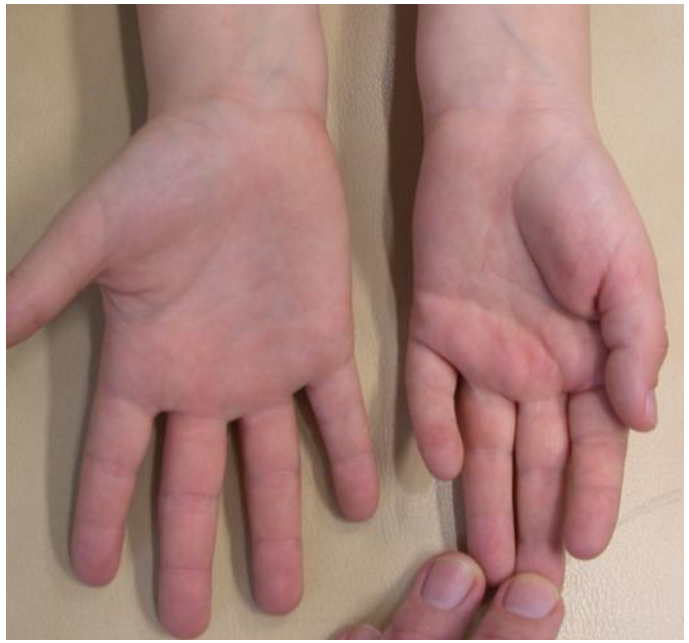


NF2 in children

- Cutaneous plaques
- Mononeuropathy
- Retinal abnormalities, cataract, epiretinal membranes
- Few café-au-lait spots: faint, irregular
- Vestibular schwannomas
  - Hearing loss
  - Vertigo
- Spinal tumors







Hum Genet (2008) 124:105–122
DOI 10.1007/s00439-008-0542-4

REVIEW ARTICLE

Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg?

Katharina Wimmer · Julia Etzler

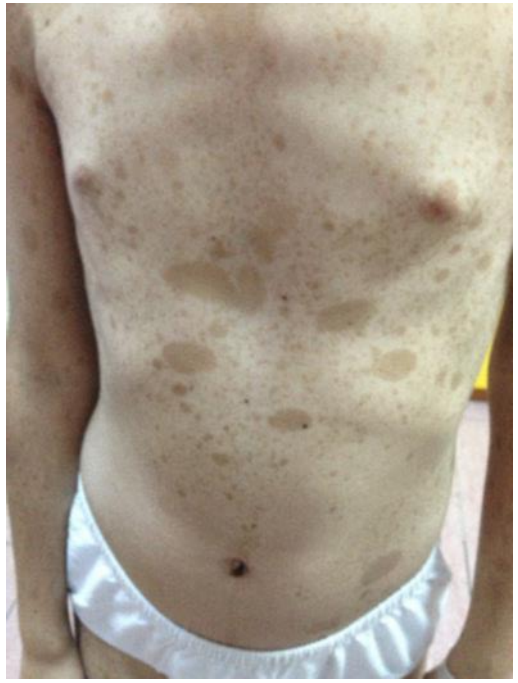
GENES, CHROMOSOMES & CANCER 52:656–664 (2013)

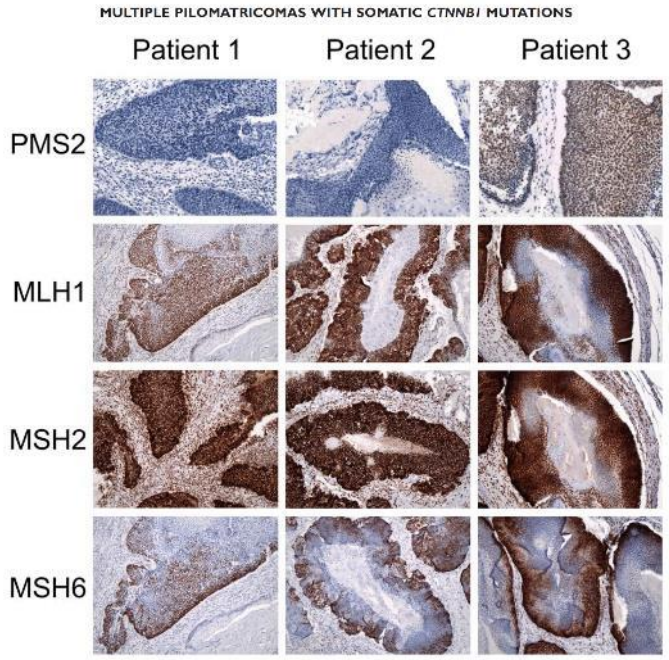
Multiple Pilomatricomas with Somatic *CTNNB1* Mutations in Children with Constitutive Mismatch Repair Deficiency

Magdalena Chmara,[1,2†] Annekatrin Wernstedt,[3†] Bartosz Wasag,[1,2] Hilde Peeters,[1,4] Marleen Renard,[5] Eline Beert,[1] Hilde Brems,[1] Tina Giner,[6] Imke Bieber,[7] Henning Hamm,[6] Raf Sciot,[8] Katharina Wimmer,[3*] and Eric Legius[1,4*]

Café-au-lait spots
consanguinity
Childhood cancer
pilomatricomas

Check MMR genes:
MLH1, MSH2, **MSH6, PMS2**
Bi-allelic mutations!





REVIEW

Constitutional mismatch repair deficiency as a differential diagnosis of neurofibromatosis type 1: consensus guidelines for testing a child without malignancy

Manon Suerink,[1] Tim Ripperger,[2] Ludwine Messiaen,[3] Fred H Menko,[4] Franck Bourdeaut,[5] Chrystelle Colas,[6,7] Marjolijn Jongmans,[8,9] Yael Goldberg,[10] Maartje Nielsen,[1] Martine Muleris,[7] Mariëtte van Kouwen,[11] Irene Slavc,[12] Christian Kratz,[13] Hans F Vasen,[14] Laurence Brugières,[15] Eric Legius,[16] Katharina Wimmer[17]

J Med Genet: first published as 10.1136/jmedgenet-201

JMG, 10 November 2018

Prerequisites

- Suspicion of NF1 due to the presence of at least one diagnostic NF1 feature*, including at least two hyperpigmented skin patches reminiscent of CALMs.
- No *NF1* and *SPRED1* germline mutations detected using comprehensive and highly sensitive mutation analysis protocols.†
- Absence of diagnostic NF1 sign(s) in both parents.‡

Additional features, at least one (either in the family or in the patient) is required

In the family

- Consanguineous parents.
- Genetic diagnosis of Lynch syndrome in one or both of the parental families.
- Sibling with diagnostic NF1 sign(s)‡.
- A (deceased) sibling§ with any type of childhood malignancy.
- One of the following carcinomas from the Lynch syndrome spectrum¶: colorectal cancer, endometrial cancer, ovarian cancer, gastric cancer, small bowel cancer, cancer of the bile duct or gall bladder, pancreatic cancer or urothelial cancer before the age of 60 years in first-degree or second-degree relative.

In the patient

- Atypical CALMs (irregular borders and/or pigmentation).
- Hypopigmented skin patches.
- One or more pilomatricoma(s) in the patient.
- Agenesis of the corpus callosum.
- Non-therapy-induced cavernoma.
- Multiple developmental vascular abnormalities (also known as cerebral venous angiomas) in separate regions of the brain.

Summary CAL spots

- NF1
  - Be aware of mosaicism! (segmental or mild generalized)
- (NF2)
  - Cutaneous schwannomas, mononeuropathy, retinal hamartomas
- Legius syndrome
  - CAL only, frequently familial, no *NF1* mutation
- McCune-Albright syndrome
  - Always mosaicism, osseous fibrous dysplasia, precocious puberty
- Piebaldism
  - White spots (thorax and forehead)
- Genetic instability syndromes (C-MMRD)
  - Childhood cancer, pilomatricomas, frequent consanguinity
- Noonan syndrome with multiple lentigines

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